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FROM O,S-DIETHYL THIOLMALONATE TO β-HYDROXYPROPIONATE AND ACRYLATE DERIVATIVES.
SYNTHETIC STUDIES OF CLOVANE-DIOL.

BY

W. M. NJUE

A THESIS
SUBMITTED TO THE FACULTY OF GRADUATE STUDIES AND RESEARCH
IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE
OF DOCTOR OF PHILOSOPHY

DEPARTMENT OF CHEMISTRY

EDMONTON, ALBERTA
SPRING, 1988

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submitted by W. M. NJUE in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Chemistry.

....
H.J. Liu, Supervisor

E. V. Black..........

George Kotovych..........

....

John Hogg..........

Zdenek Valenta..........
External Examiner

Date MAR 21 1988

To

My late parents, my wife Jane Rose,
my son Munene and daughter Mukami.

ABSTRACT

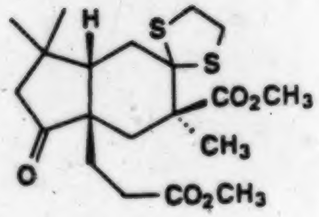
The first part of the thesis describes a convenient method for the preparation of β-hydroxypropionate and acrylate derivatives using O,S-diethyl thiolmalonate (**23**, Part I) as a common starting material. As shown in Scheme II, Part I (p. 11), thiolester **23** was found to undergo alkylation with a variety of alkyl halides under mild conditions. Selective reduction of the thiolester group of the alkylation products gave rise to ethyl β-hydroxypropionates. Subsequent dehydration resulted in the formation of ethyl acrylate derivatives. The use of thiolester **23** as a convenient source of a β-hyroxypropionate carbanion in alkylation reactions has therefore been established in this work.

The second part of this thesis describes the preparation of bicyclic keto diester **101** (Part II), a potential synthetic precursor to clovane-diol (**1**, Part II), starting from 10-camphorsulfonic acid via the route outlined in Scheme XV, Part II (p. 139). Fusion of 10-camphorsulfonic acid (**35**) with potassium hydroxide followed by esterification gave methyl campholenate (**40**) which was subjected to photooxygenation to furnish enone ester **42**. The methylidene group was removed by epoxidation followed by treatment with sodium hydroxide. Esterification of the

resulting carboxylic acid gave rise to keto ester 53 which was subjected to Michael addition with methyl acrylate to give keto diester 72. Subsequent Dieckmann condensation afforded diketo ester 73 which was methylated to give keto ester 78. Thioketalization followed by Michael addition of the resulting thioketal 92 furnished keto diester 101.

EtO_2CCH_2COSEt

23



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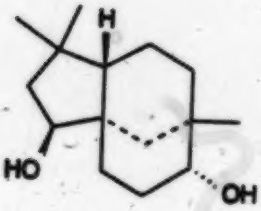

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PART I.

FROM O,S-DIETHYL THIOLMALONATE TO β-HYDROXYPROPIONATE AND ACRYLATE DERIVATIVES.

INTRODUCTION

A thiolester is a versatile functional group which has been used in organic synthesis to facilitate the formation of carbon-carbon bonds and the preparation of a number of important functionalities. The first thiolester was reported in 1875 by Muhler[1] who prepared ethyl thiolacetate from acetyl chloride and ethanethiol. In the next seventy years or so several additional methods were reported. Wallach and Bleibtreu[2] illustrated the formation of thiolacetates by the hydrolysis of thiolacetanilides. Obermeyer[3] obtained methyl thiolacetate and thiolisobutyrate by the reaction of the corresponding acid chlorides and lead methylmercaptides. Later, Wheeler[4] prepared ethyl thiolbenzoate by reacting ethyl bromide with potassium thiolbenzoate.

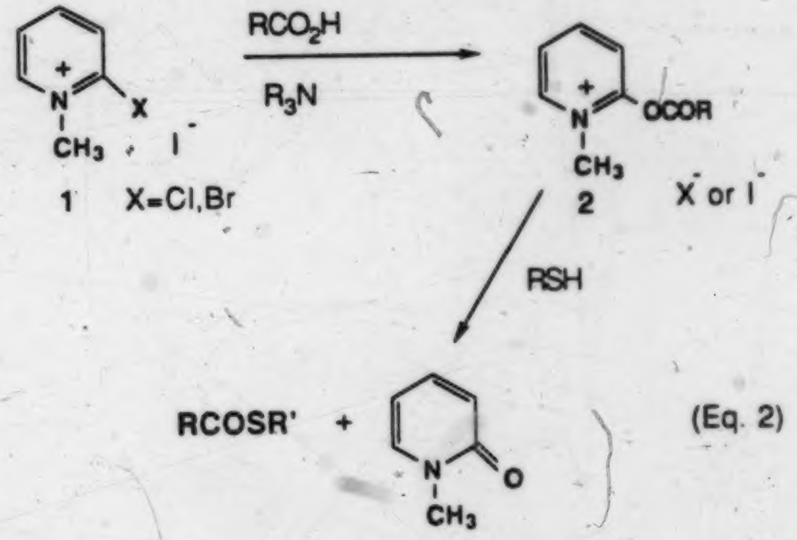
Very little attention was drawn to the chemical properties of thiolesters until the mid-1940's when Jeger and coworkers[5] examined the potential use of thiolesters in the modification of steroids. They showed that Raney nickel promoted reductive desulfurization of the thiolester functional group into a primary alcohol. In an attempt to extend this desulfurizing action of Raney nickel to the synthesis of aldehydes, Wolfrom and Karabinos[6] also investigated the reduction of thiolesters. They succeeded in the preparation of benzaldehyde and propionaldehyde from the corresponding thiolesters. A couple of years later, McIntosh _et al_.[7,8] reexamined the reduction of thiolesters and observed that, whereas the standard Raney nickel effected the conversion of thiolesters to the corresponding alcohols, deactivated Raney nickel (e.g. in boiling acetone) gave rise to aldehydes as major products.

Prior to 1970, the progress in the chemistry of thiolesters was rather slow.[9] Since then the use of thiolesters has grown significantly due to their widely spread applications as useful intermediates in organic synthesis.[10]

In 1974 Mukayama and coworkers[11] prepared thiolesters in high yields by treatment of trimethylsilyl sulfides with carboxylic esters in the presence of aluminum chloride (Eq. 1).

$$\mathrm{RCOOR} + \mathrm{(CH_3)_3SiSR'} \xrightarrow{\mathrm{AlCl_3}} \mathrm{RCOSR'} \qquad \text{(Eq.1)}$$

Mukayama[12] also showed that onium salts of aza arenes (e.g. 2-halogenated pyridinium salts 1) could be used to activate carboxylic acids (Eq. 2). The intermediates 2 thus formed reacted readily with a variety of thiols under practically neutral conditions giving high yields of the corresponding thiolesters.



In recent years, several methods have been developed for the direct transformation of carboxylic acids to the corresponding thiolesters using various activating agents. N,N-Dimethylphosphoramidic dichloride (**3**)[13] and phenylphosphorodichloridate (**4**)[14] have been shown in our laboratory to be excellent activating agents which facilitate the formation of thiolesters under very mild conditions. Other activating agents successfully studied include diethylphosphorocyamidate (**5**),[15] diphenylphosphorazidate (**6**),[16] N,N-bis(2-oxo-3-oxazolidinyl)phosphorodiamidic chloride (7)[17] and 1-fluoro-2,4,6-trinitrobenzene (8).[18]

Me_2NPOCl_2

3

$PhOPOCl_2$

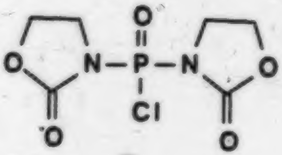
4

$CNPO(OEt)_2$

5

$N_3PO(OPh)_2$

6



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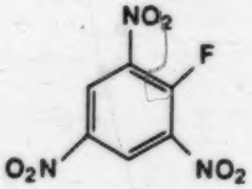

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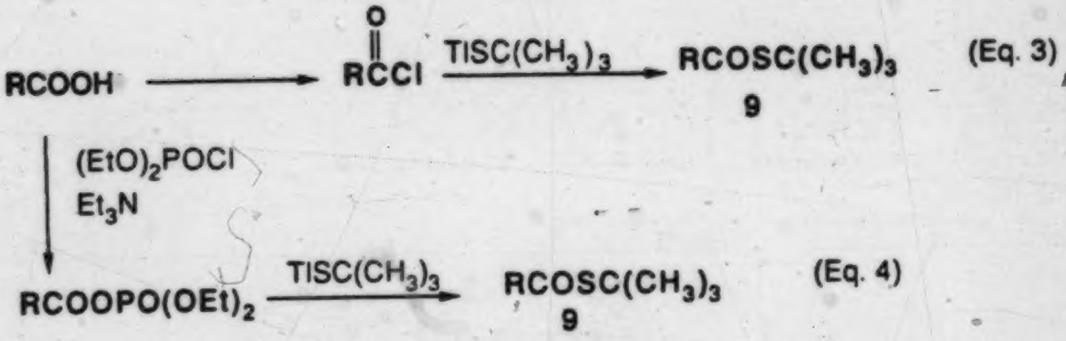
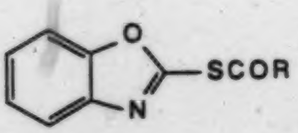
A number of indirect methods for the preparation of thiolesters have also been developed. Masamune et al.[19,20] prepared S-t-butyl thiolesters 9 from the corresponding acids by treatment of intermediate acid chlorides (Eq. 3) or mixed acid anhydrides (Eq. 4) with thallous 2-methylpropane-2-thiolate. In another method, Ueda and coworkers[21] employed S- and N-acyl derivatives (10 and 11) of 2-mercaptobenzoxazole as intermediates. These compounds were found to be highly reactive acylating



$$\mathrm{RCOOH} \longrightarrow \mathrm{R\overset{O}{\overset{\|}{C}}Cl} \xrightarrow{\mathrm{TlSC(CH_3)_3}} \underset{\mathbf{9}}{\mathrm{RCOSC(CH_3)_3}} \qquad \text{(Eq. 3)}$$

$$\mathrm{RCOOH} \xrightarrow[\mathrm{Et_3N}]{\mathrm{(EtO)_2POCl}} \mathrm{RCOOPO(OEt)_2} \xrightarrow{\mathrm{TlSC(CH_3)_3}} \underset{\mathbf{9}}{\mathrm{RCOSC(CH_3)_3}} \qquad \text{(Eq. 4)}$$

agents, apparently due to the electron withdrawing character of the benzoxazole ring system. Imidazolides **12** and 1,2,4-triazolides **13** were also shown to be excellent acylating agents which gave rise to thiolesters in high yields upon treatment with mercaptans.[22]



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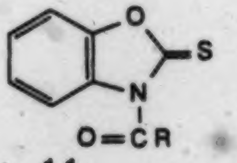

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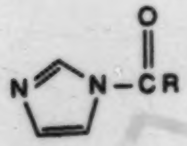

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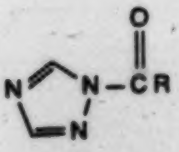

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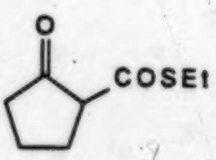
Thiolester has emerged as a highly useful functional group in organic synthesis. Based on its interesting reactivities, a large number of synthetic methods have been developed recently. Several examples are illustrated below.

The best known example is probably the use of the ω-hydroxy thiolester system to induce the formation of medium and large lactone rings,[23-27] which are present in a variety of natural products.[24,28,29] Dithiolesters have been shown to undergo Dieckmann condensation under conditions substantially milder than those required for the oxygen analogues. The cyclization of S,S-diethyl dithioladipate (**14**),[30] for instance, occurred smoothly within 2 h when treated with sodium hydride in 1,2-dimethoxyethane at room temperature in the presence of a catalytic amount of ethanethiol to give a 91% yield of S-ethyl 2-cyclopentanonecarbonylthioate (15).

$EtSOC(CH_2)_4COSEt$

14



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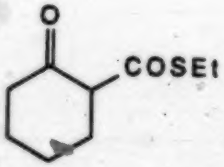

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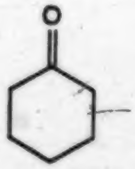
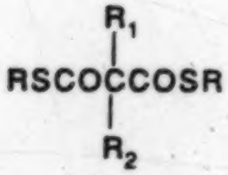


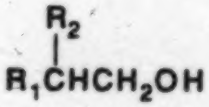
17

Interestingly, unlike simple thiolesters which gave rise to alcohols or aldehydes on treatment with Raney nickel, β-keto thiolesters were found to undergo complete dealkylthiolcarbonylation (e.g. 16 → 17).[30,31] Extrapolation of these results suggests that Raney nickel reduction of dithiolmalonate derivatives **18** could lead to the formation of ethanol derivatives **19**. This expectation was realized experimentally and S,S'-diethyl dithiolmalonate **20** was used successfully as an ethanol carbanion equivalent in alkylation and Michael reactions.[32,33]



$RSCO\overset{R_1}{\underset{R_2}{C}}COSR$

18



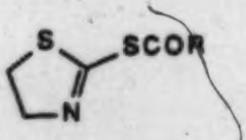
$R_1\overset{R_2}{C}HCH_2OH$

19

$EtSOCCH_2COSEt$

20

Another useful property of the thiolester group is its high reactivity towards metal hydride reducing agents. Fujita et al.[34] observed that the highly reactive thiolester **21** derived from 2-mercaptothiazoline could be reduced to the alcohol level by sodium borohydride. It



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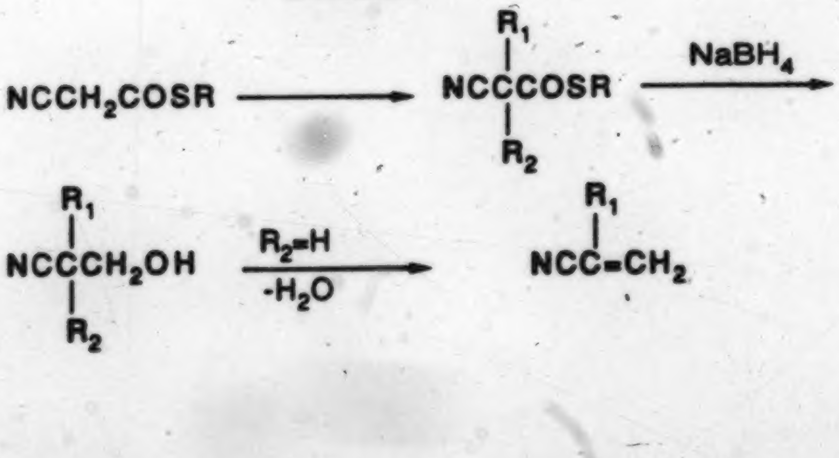
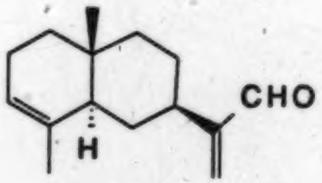
was later found that the reduction of ordinary thiolesters was equally facile and could be selectively accomplished in the presence of commonly encountered acid derivatives such as amides, esters and nitriles.[35]

The ease of reduction of thiolester group with sodium borohydride suggests a number of interesting possibilities for its use as a latent hydroxymethyl unit in synthesis, especially when such a unit, with or without protection, can not be directly involved in a synthetic transformation. Accordingly, a convenient synthetic approach to β-hydroxypropionitrile and acrylonitrile derivatives has been developed involving alkylation, Michael addition or Knovenagel-type reactions of cyanothiolacetate, as the initiating step.[36,37] As shown in Scheme I, the synthetic approach is greatly facilitated because of the ability of the thiolester group present in the starting material to serve both as an activating group for the carbon-carbon

Scheme I



bond formation and as a convenient source of the hydroxymethyl moiety. The overall transformation can be considered as the replacement of one or two α-protons of β-hydroxypropionitrile (or acrylonitrile) by electrophiles using cyanothiolacetate as a β-hydroxypropionitrile carbanion equivalent. This method, which in essence provides a convenient means for the incorporation of a highly functionalized isopropyl unit, has been successfully applied as a key step to the synthesis of α-costal (**22**).[38]



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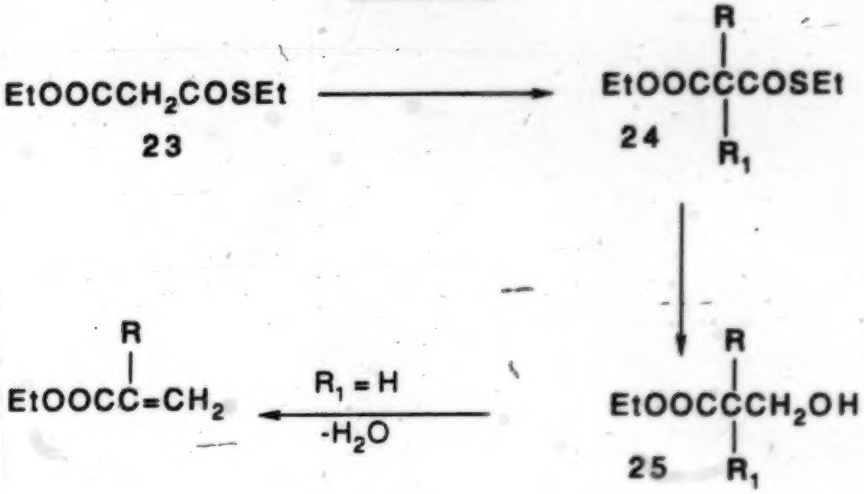
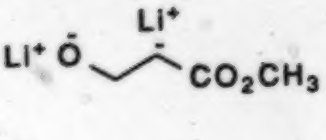
In continuation of our investigation of the application of the thiolester group as a latent hydroxymethyl unit in synthesis, we have studied the use of O,S-diethyl thiolmalonate (**23**) as a convenient source of β-hydroxypropionate carbanion to facilitate the synthesis of β-hydroxypropionate and acrylate derivatives. As shown in Scheme II, thiolmalonate **23** is expected to undergo substitution reactions with electrophiles such as alkyl halides (**23** → **24**). Selective reduction of the thiolester

Scheme II



group (**24** → **25**) would provide a simple entry to β-hydroxypropionates. In case of monosubstituted β-hydroxypropionates, subsequent dehydration should lead to acrylate formation.

The preparation of β-hydroxypropionate derivatives by displacement of an α-hydrogen of the parent molecule and its homologues has been the subject of considerable interest. Schlessinger and Herrmann[39] observed that treatment of methyl β-hydroxypropionate with two equivalents of lithium diisopropylamide gave rise to the corresponding dianion (**26**). They also showed that the dianion so generated reacted with electrophiles in a highly regioselective manner involving predominantly the carbanion. The generality of the method is apparent from the formation of a large number of substituted β-hydroxypropionates **27** in high yields using various alkyl halides and dimethyl disulfide. This direct substitution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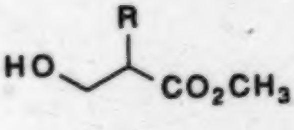
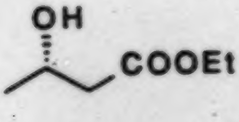

27

was further investigated by Fräter[40,41] and Seebach,[42,43] involving homologous β-hydroxypropionates. In their studies, a high degree of stereoselectivity (wherever applicable) was also observed. For example, methylation of the dianion generated from (3S)-ethyl 3-hydroxybutanoate (**28**) with lithium diisopropylamide gave rise to a 67% yield of (2S,3S)- (**29**) and (2R,3S)-ethyl 3-hydroxy-2-methylbutanoate (**30**) in the ratio of 19:1 in favour of the former product. The predominant formation of the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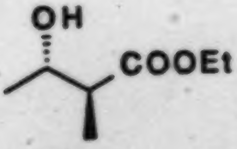
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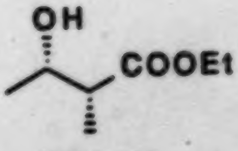
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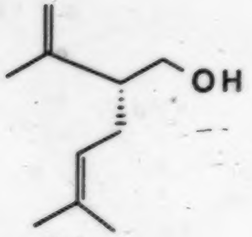
threo isomer has been consistently observed for a number of alkylation reactions. This method has been used in the synthesis of lavandulol (**31**),[44] a monoterpenoid alcohol, and compound **32**,[45] the enantiomer of the pheromone isolated from smaller European bark beetle (Scolytus multistriatus).



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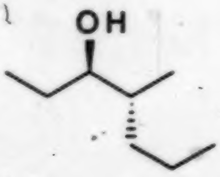
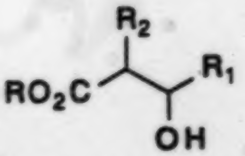


32

The above alkylation procedure leading to β-hydroxypropionate derivatives has the obvious advantage of being direct and stereoselective. Unfortunately, the method has the following practical limitations. The generation of a dianion requires a powerful base which is not compatible with many frequently encountered functional groups. Furthermore, the introduction of a second substituent to the α-carbon (e.g. **33** → **34**) was shown to be difficult. It



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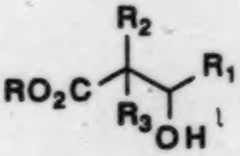
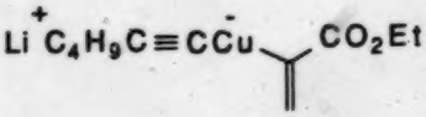


34

appears that the reaction proceeds only with methyl and allyl halides. Even with these highly reactive reagents, the yields of the products were only modest (~50%).[40]

Alkylation of an intact unit of acrylate has also been reported.[46,47] Lithium α-ethoxycarbonylvinyl(hex-1-ynyl)cuprate (**35**) was prepared from ethyl α-bromoacrylate and lithium hexynylmethylcuprate. This complex was found to undergo alkylation with allyl halides to give products **36** in modest yields (50%-70%).[46] This reagent, however,



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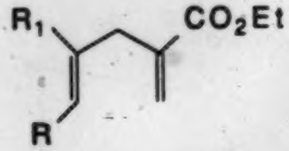

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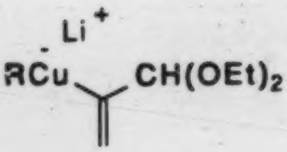
has only modest reactivity and it does not undergo reactions with alkyl halides nor with benzyl bromide. In approaches to synthesis of acrylate derivatives, several acrylate equivalents have also been used successfully. Ficini and others[48-52] prepared cuprates **37** from α-bromoacrolein diethyl acetal (**38**). These copper reagents were found to react with a number of electrophiles. The addition of reagent **39** to the enone **40**, for example,



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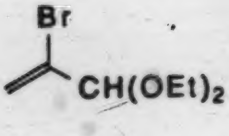

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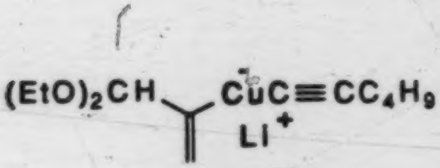
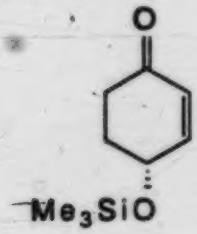


39

gave rise to Michael adduct **41** in 93% yield.[49] Subsequent hydrolysis and oxidation led to the formation of acrylic acid derivative **42**. In another approach, methyl β-(N,N-dimethylamino)propionate (**43**) was used as a latent acrylate unit.[53] Treatment of **43** with lithium diisopropylamide followed by alkylation of the resulting enolate ion gave rise to monosubstituted products **44**. Alkylating agents used include methyl, allyl and several other primary alkyl halides. The yields were in the range of 57% to 88%. N-Methylation of β-aminopropionates **44** followed by base-induced elimination resulted in the formation of 2-substituted acrylates **45**.

The first part of this thesis describes a new method for the preparation of β-hydroxypropionates and acrylate derivatives using O,S-diethyl thiolmalonate as a convenient source of masked ethyl β-hydroxypropionate carbanion. This method, which has been developed on the basis of the principle outlined in Scheme II, is operationally simple and apparently general. Furthermore, it makes use of mild reaction conditions which are compatible with many commonly encountered functional groups. These salient features warrant its broad utility in organic synthesis.



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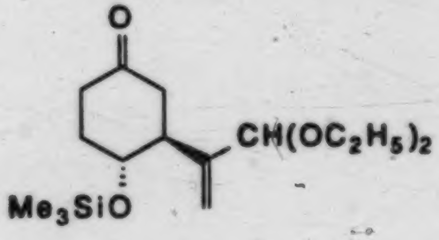

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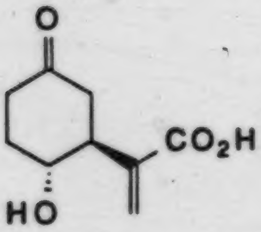

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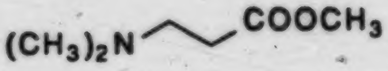

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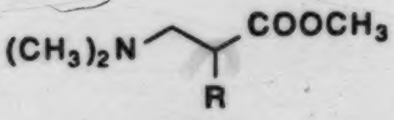

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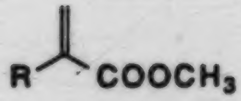


45

RESULTS AND DISCUSSION

O,S-Diethyl thiolmalonate (**23**), used in the present studies, was prepared from the commercially available ethyl malonyl chloride (**46**) by treatment with an excess of ethanethiol (1.5 equivalents) at room temperature for

EtO_2CCH_2COSEt $\qquad$ $CH_3CH_2O_2CCH_2COCl$

23 $\qquad$ **46**

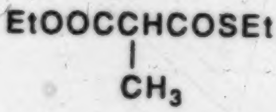
24 h. The O,S-diethyl thiolmalonate (**23**) thus obtained was purified by distillation at 60°C/1 torr followed by flash chromatography[54] on silica gel using a solution of 20% ether in petroleum ether as an eluent. Pure thiolmalonate **23** was isolated in near quantitative yield and could be stored in the refrigerator for a prolonged period of time without apparent decomposition. Thiolmalonate **23** displayed absorption bands in the ir spectrum at 1742 and 1688 cm^{-1} for the O- and S-ester functionalities, respectively. These characteristic absorption bands were generally observed for all the substitution products (vide infra) derived from this compound with small differences in exact positions. The nmr spectrum showed a singlet at δ 3.57 for the methylene hydrogens adjacent to the carbonyl groups. In addition, two pairs of ethyl signals

were observed, one at δ 4.20 (q, 2H, J = 8 Hz) and 1.29 (t, 3H, J = 8 Hz), and the other at δ 2.95 (q, 2H, J = 8 Hz) and 1.28 (t, 3H, J = 8 Hz). The former pair was assigned to the ethoxy moiety and the latter to the thioethoxy group. These ethyl signals were commonly observed for all the compounds prepared from **23** in the current studies. The mass spectrum of thiolmalonate **23** showed a molecular ion peak at m/z 176.0509 in accord with the required formula of $C_7H_{12}O_3S$.

The feasibility of the general synthetic approach to β-hydroxypropionate and acrylate derivatives (Scheme II) depends on the ability of thiolmalonate **23** to undergo reaction with various electrophiles such as alkyl halides. The methylene protons of thiolester **23**, which are adjacent to the two electron-withdrawing carbonyl groups, are expected to be strongly acidic. The acidity of **23**, which remains to be determined, should be comparable to that of diethyl malonate which has a pKa value of 13.3. Indeed thiolmalonate **23** could easily be deprotonated with a variety of bases. The carbanion thus generated was found to undergo alkylation with a variety of alkyl halides. Details are described below. Also discussed are successful transformations of the alkylation products to β-hydroxypropionates and acrylic esters.

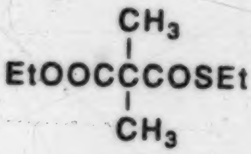
1. Alkylation of O,S-diethyl thiolmalonate (23)

Thiolmalonate **23** could easily be deprotonated with sodium hydride. When the anion was subjected to reactions with alkyl halides in tetrahydrofuran at temperatures ranging from 20°C to ~70°C, alkylation products were obtained in good yields. For monoalkylation, the incorporation of a simple alkyl group could be controlled by the use of stoichiometric amounts (or slight excess) of the reagents. Thus, treatment of thiolmalonate **23** with 1.1 equivalents of sodium hydride and 1.0 equivalent of methyl iodide in tetrahydrofuran at room temperature for 3 h gave rise to methyl derivative **47** in 80% yield. A small amount (11%) of dialkylation product **48** was also obtained. The ir and nmr spectra of compound **47** showed characteristic signals (vide supra) for the ester and thiolester groups. The nmr spectrum also displayed a quartet at δ3.65 for one hydrogen and a methyl doublet at δ 1.50, each with a coupling constant of 7.5 Hz. The structure was further confirmed by the mass spectrum showing a molecular ion peak at 190.0657. With more



$\mathrm{EtOOC}\underset{\mathrm{CH_3}}{\mathrm{CH}}\mathrm{COSEt}$

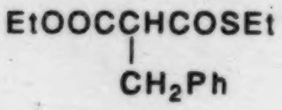
47



$\mathrm{EtOOC}\overset{\mathrm{CH_3}}{\underset{\mathrm{CH_3}}{\mathrm{C}}}\mathrm{COSEt}$

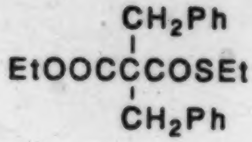
48

reactive alkyl halides the formation of dialkylation products in small quantity could not be suppressed. Alkylation of **23** with benzyl bromide (2[illegible]C, 4 h) gave rise to a 72% yield of the desired product **49** along with 2% of the dialkylation product **50**. Similarly, treatment of the sodium salt of **23** with methyl 3-bromopropionate gave a mixture of mono- and dialkylation products **51** and **52** in



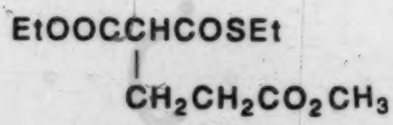
$\mathrm{EtOOC}\underset{\mathrm{CH_2Ph}}{\underset{|}{\mathrm{C}}}\mathrm{HCOSEt}$

49



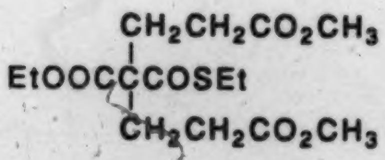
$\mathrm{EtOOC}\overset{\mathrm{CH_2Ph}}{\overset{|}{\underset{\mathrm{CH_2Ph}}{\underset{|}{\mathrm{C}}}}}\mathrm{COSEt}$

50



$\mathrm{EtOOC}\underset{\mathrm{CH_2CH_2CO_2CH_3}}{\underset{|}{\mathrm{C}}}\mathrm{HCOSEt}$

51

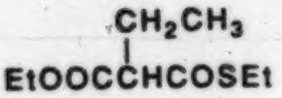


$\mathrm{EtOOC}\overset{\mathrm{CH_2CH_2CO_2CH_3}}{\overset{|}{\underset{\mathrm{CH_2CH_2CO_2CH_3}}{\underset{|}{\mathrm{C}}}}}\mathrm{COSEt}$

52

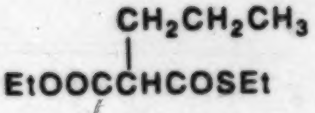
8:1 ratio in a total yield of 74%. Compounds **49** and **51** were readily identified on the basis of the spectral data. Other than the signals generally observed for thiolester and ester groups, the ir spectrum of **49** showed additional absorption bands at 1604 and 1584 cm^{-1} for the phenyl group. In the nmr spectrum a 5H multiplet at δ 7.22, a 1H triplet (J = 8 Hz) at δ 3.84 and two 1H doublets (J = 8 Hz each) at δ 3.22 and 3.25 could readily be assigned to the phenylethyl unit. In the case of compound **51**, the nmr spectrum displayed the following additional signals: a methyl signal at δ 3.68, a 1H triplet (J = 7 Hz) at δ 3.65, a 2H triplet (J = 7 Hz) at δ 2.38 and a 2H doublet of triplets (J = J' = 7 Hz) at δ 2.24. These signals were due to the propionate unit present in the molecule. In confirmation of the structural assignment, compound **49** showed a molecular ion peak at 266.0975. The molecular ion peak of compound 51 was not detected. Instead, an ion peak appeared at m/z 231.0686 (M^+-31) due to the loss of a methoxy unit.

With less reactive alkylating agents, the alkylation proceeded much slower as expected. At the same time, under the conditions applied, the dialkylation was not detected. For example, the alkylation of thiolmalonate **23** with ethyl iodide, carried out at room temperature in tetrahydrofuran gave a 90% yield of the desired ethyl derivative **53** as the sole product after 20 h. The nmr spectrum of the compound showed the presence of a n-propyl unit with a methyl triplet at δ 0.96 (J = 7.5 Hz), a methylene quintet at δ 1.98 (J = 7.5 Hz) and a methine triplet at δ 3.46 (J = 7.5 Hz). In the mass spectrum the expected molecular ion peak was observed at m/z 204.0824. The reaction of thiolmalonate



$\mathrm{EtOOC\overset{\overset{\displaystyle CH_2CH_3}{|}}{C}HCOSEt}$

53

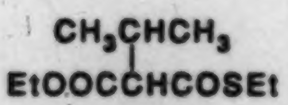


$\mathrm{EtOOC\overset{\overset{\displaystyle CH_2CH_2CH_3}{|}}{C}HCOSEt}$

54

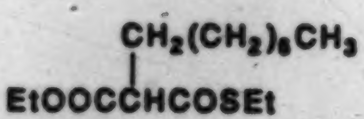
23 and 1-iodopropane was carried out under similar conditions. After 8 h, compound 54 was produced in 82% yield. The nmr spectrum showed signals at δ 0.92 (t, 3H, J = 8 Hz), 1.35 (m, 2H, J = 7 Hz), 1.90 (q, 2H, J = 7 Hz) and 3.54 (t, 1H, J = 7 Hz) due to a 1,1-disubstituted butane. In agreement with the structural assignment, the mass spectrum displayed a molecular ion peak at m/z 218.0974.

The alkylation of thiolmalonate 23 with isopropyl iodide was found to be extremely slow at room temperature. At refluxing temperature, however, the reaction occurred quite readily to give a 91% yield of compound 55 which showed, in the nmr spectrum, a multiplet at δ 2.48 and a doublet (J = 9 Hz) at δ 3.28 integrating to one hydrogen each, and two methyl doublets (J = 7 Hz each) at δ 0.96 and 0.98. In the mass spectrum, a molecular ion peak appeared at m/z 218.0978 as expected.



$\mathrm{EtOOC\overset{\overset{\displaystyle CH_3CHCH_3}{|}}{C}HCOSEt}$

55



$\mathrm{EtOOC\overset{\overset{\displaystyle CH_2(CH_2)_8CH_3}{|}}{C}HCOSEt}$

56

Sequential treatment of thiolester **23** with sodium hydride and n-octyl bromide in refluxing tetrahydrofuran for 24 h gave rise to compound **56** in 56% yield along with a 29% recovery of the starting material. When the same reaction was carried out in the presence of a catalytic amount of sodium iodide (0.1 eq.), an improved yield (84%) of **56** was obtained with complete consumption of starting material. The nmr spectrum of this compound showed a methyl triplet (J = 7 Hz) at δ 0.87 and an unresolved multiplet centered at δ 1.28 for a total of eighteen protons. Other signals observed include three quartets at δ 1.90, 2.92 and 4.20, each with a coupling constant of 7 Hz and integrating to two protons, and a triplet at δ 3.54 also with a coupling constant of 7 Hz for the methine proton. The assigned structure was confirmed by the mass spectrum which showed a peak at m/z 288.1760 for the molecular ion.

Dialkylation of thiolmalonate **23** was found to be equally facile. For the incorporation of two identical substituents, the reaction could be easily carried out using adequate amount of alkylating agent and base. The conversion of **23** to dimethyl derivative **48**, for example, was effected by treatment of the former compound with 3.0

equivalents of sodium hydride* and 2.1 equivalents of methyl iodide in tetrahydrofuran for 4 h. The product **48** thus obtained in 97% yield showed characteristic absorption bands in the ir spectrum for the ester and thiolester groups at 1739 cm^{-1} and 1682 cm^{-1}, which were generally observed for this series of compounds. Other than those characteristic signals due to ethoxy and thioethyl moieties (vide supra), the nmr spectrum displayed a singlet at δ 1.48 for the gem-dimethyl. The structure was further verified by the mass spectrum showing a molecular ion peak at m/z 204.0818. Dialkylation of thiolester **23** was also carried out with ethyl iodide, n-propyl iodide, n-butyl iodide using similar reaction conditions. The expected products **57, 58** and **59** were isolated in consistently high yields (81-90%). In all these cases, the structures were readily deduced on the basis of the spectral data.**

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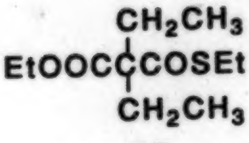
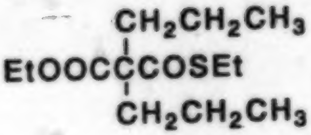
* When a lesser amount of sodium hydride was used, the reaction was found to be incomplete even after an extended period of time. These results suggested that the percentage of sodium hydride used was lower than indicated.

** See Experimental for details.



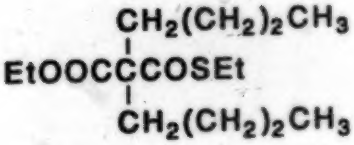
$$\mathrm{EtOOC\overset{CH_2CH_3}{\underset{CH_2CH_3}{C}}COSEt}$$

57



$$\mathrm{EtOOC\overset{CH_2CH_2CH_3}{\underset{CH_2CH_2CH_3}{C}}COSEt}$$

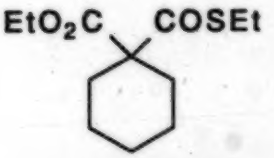
58



$$\mathrm{EtOOC\overset{CH_2(CH_2)_2CH_3}{\underset{CH_2(CH_2)_2CH_3}{C}}COSEt}$$

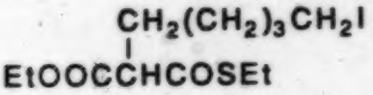
59

Reaction of thiolester **23** with an alkyl dihalide could, in principle, lead to the formation of a cyclic compound. This cyclization process has been demonstrated with 1,5-diiodopentane. Treatment of **23** with sodium hydride (3.0 eq.) and 1,5-diiodopentane (1.2 eq.) in tetrahydrofuran at room temperature for 24 h gave rise to cyclic compound **60** in 56% yield along with recovered starting material (20%) and a small amount of unidentified



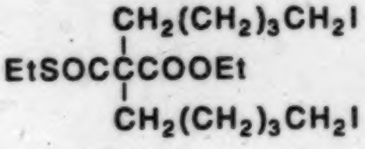
60

products. Compound **60** showed a molecular ion peak at m/z 244.1133 in the mass spectrum and three broad multiplets centered at δ 1.48 (6H), 1.90 (2H) and 2.15 (2H) in the nmr spectrum due to the cyclohexyl hydrogens. In an attempt to improve the yield of **60**, the reaction was carried out using 4.0 equivalents of sodium hydride. In this case, the starting material was completely consumed in 30 h and the desired product was isolated in 67% yield. Analysis of the remaining material indicated the



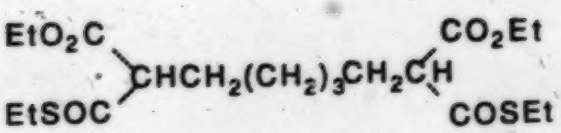
$\mathrm{EtOOC\overset{CH_2(CH_2)_3CH_2I}{\overset{|}{C}}HCOSEt}$

61



$\mathrm{EtSOC\underset{\underset{|}{CH_2(CH_2)_3CH_2I}}{\overset{CH_2(CH_2)_3CH_2I}{\overset{|}{C}}}COOEt}$

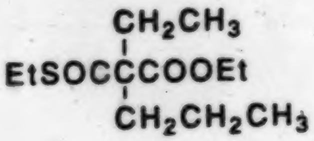
62



63

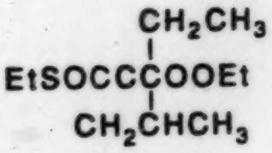
presence of three additional products. These compounds were identified as uncyclized iodo compound **61** (10%), dialkylation product **62** (4%) and dimeric compound **63** (20%). Iodo compound **61** showed, in the mass spectrum, a molecular ion peak at m/z 372.0259 and, in the nmr spectrum, a triplet at 3.18 (2H, J = 7 Hz) for the methylene group bearing the iodine. On treatment with sodium hydride (2.0 equivalents) in tetrahydrofuran for 24 h, this compound was further cyclized to give an additional amount of **60** in 97% yield. The nmr spectrum of 62 displayed a 4H triplet at δ 3.18 for the iodo methylene groups. Its structure was further confirmed by mass spectrum showing the required molecular ion peak at m/z 568.1192. A consistent molecular ion peak was also observed for the dimeric compound 63.

For the preparation of O,S-diethyl thiolmalonates possessing two non-identical substituents, the introduction of the second group could also be carried out with ease as exemplified below. Treatment of ester 53 with n-propyl iodide (1.2 eq.) and sodium hydride (1.5 eq.) in refluxing tetrahydrofuran for 2 h gave rise to the desired product 64 in 91% yield. Under similar conditions the reaction of 53 with isopropyl iodide afforded an 87% yield of compound 65. These products were readily identified spectroscopically.*



$$\mathrm{EtSOC}\overset{\mathrm{CH_2CH_3}}{\underset{\mathrm{CH_2CH_2CH_3}}{\mathrm{C}}}\mathrm{COOEt}$$

64



$$\mathrm{EtSOC}\overset{\mathrm{CH_2CH_3}}{\underset{\mathrm{CH_2CHCH_3}}{\mathrm{C}}}\mathrm{COOEt}$$

65

The results obtained from alkylation reactions are further summarized in Table I.

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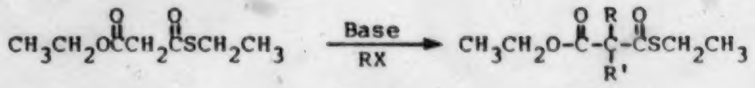
* See Experimental for details.

Table I. Alkylation of O,S-Diethyl Thiolmalonate.



$$CH_3CH_2O\overset{O}{\overset{\|}{C}}CH_2\overset{O}{\overset{\|}{C}}SCH_2CH_3 \xrightarrow[RX]{Base} CH_3CH_2O-\overset{O}{\overset{\|}{C}}-\underset{R'}{\overset{R}{C}}-\overset{O}{\overset{\|}{C}}SCH_2CH_3$$

Entry	Alkylating Agent (Equiv.)	Base (Equiv.) Solvent	Time (h)	Temp. °C	Products mono	Products di	% Yield[a] mono	% Yield[a] di	Recovered Thiolester **23**
1	CH_3I (1.0)	NaH (1.1) THF	3	r.t.	$R=CH_3$, $R'=H$ **47**	$R=R'=CH_3$ **48**	80	11	-
2	CH_3I (2.1)	NaH (3.0) THF	4	r.t.		**48**	-	97	-
3	$PhCH_2Br$ (1.1)	NaH (1.3) THF	4	r.t.	$R=PhCH_2$, $R'=H$ **49**	$R=R'=PhCH_2$ **50**	72	2	16
4	$CH_3O\overset{O}{\overset{\|}{C}}CH_2CH_2Br$ (1.1)	NaH (1.3) THF	12	r.t.	$R=CH_3O\overset{O}{\overset{\|}{C}}CH_2CH_2$, $R'=H$ **51**	$R=R'=$ $CH_3O\overset{O}{\overset{\|}{C}}CH_2CH_2$ **52**	66	8	12
5	CH_3CH_2I (1.2)	NaH (1.5) THF	14	r.t.	$R=CH_3CH_2$, $R'=H$ **53**		90	-	-
6	$CH_3CH_2CH_2I$ (1.1)	NaH (1.2) THF	8	r.t.	$R=CH_3CH_2CH_2$ $R'=H$ **54**		82	-	9

continued...

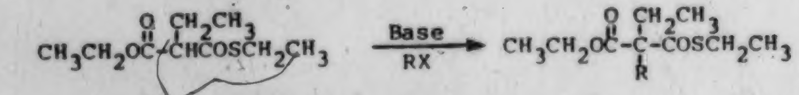
Table I (continued):

Entry	Alkylating Agent (Equiv.)	Base (Equiv.) Solvent	Time (h)	Temp. °C	Products mono	Products di	% Yield[a] mono	% Yield[a] di	Recovered Thiolester **23**
7	$(CH_3)_2CHI$ (1.2)	NaH (1.5) THF	20	reflux	R=$(CH_3)_2CH$, R'=H **55**		91	-	-
8	$CH_3(CH_2)_7Br$ (1.1)	NaH (1.3) THF	24	reflux	R=$CH_3(CH_2)_7$ R'=H **56**		55	-	29
9	$CH_3(CH_2)_7Br$ (1.2)	NaH (1.5) THF NaI (cat.)	24	reflux	**56**		70	-	19
10	CH_3CH_2I (2.5)	NaH (3.0) THF	6	r.t.		R=R'=CH_3CH_2 **57**	-	82	-
11	$CH_3CH_2CH_2I$ (2.5)	NaH (3.0) THF	12	r.t.		R=R'=$CH_3CH_2CH_2$ **58**	-	90	-
12	$CH_3(CH_2)_3I$ (2.5)	NaH (3.0) THF	24	r.t.		R=R'= $CH_3(CH_2)_3$ **59**	-	81	-
13	$I(CH_2)_5I$ (1.3)	NaH (3.0) THF	24	r.t.	R=$I(CH_2)_5$, R'=H **62**	R,R'=$(CH_2)_5$ **60**	13	56	20

continued...

Table I (continued):

Entry	Alkylating Agent (Equiv.)	Base (Equiv.) Solvent	Time (h)	Temp. °C	Products mono	Products di	% Yield[a] mono	% Yield[a] di	Recovered Thiolester 23
14	$I(CH_2)_5I$ (1.2)	NaH (4.0) THF	30	r.t.	**61**	**60**	10	67	-
15	$\mathrm{EtO\overset{O}{\overset{\|}{C}}-\overset{(CH_2)_5I}{CH}\underset{O}{C}SEt}$	NaH (1.5) THF	24	r.t.		**60**	-	97	-



$$\mathrm{CH_3CH_2O\overset{O}{C}-\overset{CH_2CH_3}{CH}COSCH_2CH_3} \xrightarrow[RX]{Base} \mathrm{CH_3CH_2O\overset{O}{C}-\underset{R}{\overset{CH_2CH_3}{C}}-COSCH_2CH_3}$$

53

Entry	Alkylating Agent (Equiv.)	Base (Equiv.) Solvent	Time (h)	Temp. °C	Products mono	Products di	% Yield[a] mono	% Yield[a] di	Recovered Thiolester 23
16	$CH_3CH_2CH_2I$ (1.2)	NaH (1.5) THF	20	reflux	$R=CH_3CH_2CH_2$ **64**		91	-	-
17	$(CH_3)_2CHI$	NaH (1.5) THF	20	reflux	$R=(CH_3)_2CH$ **65**		87	-	-

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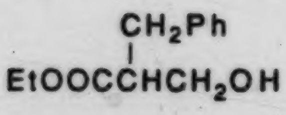
[a] Yields were based on the amount of starting material used.

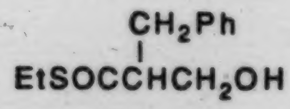
2. Selective reduction of alkylation products to β-hydroxypropionates

For the preparation of β-hydroxypropionates via O,S-diethyl thiolmalonate derivatives, attempts were initially made to reduce the thiolester group selectively to the alcohol level using sodium borohydride. Previously, it was shown in our laboratory that the thiolester group could be reduced preferentially in the presence of an O-ester moiety with sodium borohydride. Unfortunately, in the present case, the reduction was found to be non-selective. Under various conditions both thiolester and ester groups were invariably reduced. For example, the reduction of benzyl compound **49** with sodium borohydride in ethanol at 0°C for 14 h resulted in the formation of a ca. 3:1 mixture of β-hydroxypropionate **66** and β-hydroxythiolpropionate **67** in 70% yield along with a 20% yield of diol **68**. The unexpected reduction of O-ester group with sodium borohydride could be attributed to its enhanced reactivity due to the presence of an electron-withdrawing group.



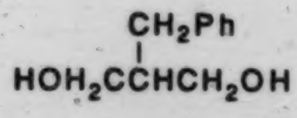
$EtOOC\overset{CH_2Ph}{\overset{|}{C}}HCH_2OH$

66



$EtSOC\overset{CH_2Ph}{\overset{|}{C}}HCH_2OH$

67



$HOH_2C\overset{CH_2Ph}{\overset{|}{C}}HCH_2OH$

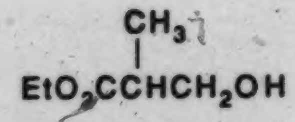
68

In search of adequate methods for the required selective reduction, the use of Raney nickel as reducing agent was examined. Previously, it was shown that Raney nickel reduction of β-keto thiolesters resulted in complete removal of the thiolester group.[30] It was also found that similar reduction of dithiolmalonates gave rise to ethanol derivatives resulting from the removal of one thiolester group and the reduction of the remaining one to the alcohol level.[31] To our delight however, in the present case, the thiolester group of thiolmalonate was reduced to the alcohol level without apparent cleavage of the carbon-carbon bond. This was probably because, unlike ketone and thiolester, an O-ester functional group was insufficient to activate the carbon-carbon bond cleavage. Thus, the thiolester group in thiolmalonate behaved normally. More importantly, Raney nickel could serve as effective reagent for the desired conversion of thiolmalonates to β-hydroxypropionates. In a typical experiment, thiolmalonate **49** was dissolved in benzene, and W-2 Raney nickel,[55] which was prewashed with benzene to remove ethanol, was added. The solution was then stirred at room temperature for 4 h. This was followed by careful filtration and extensive washing of the residue with ethanol. Bulb-to-bulb distillation of the crude product gave β-hydroxy propionate **66** in 93% yield. The ir spectrum showed characteristic absorption bands at 3445 (hydroxyl), 1732 (ester), 1580 and 1600 cm^{-1} (phenyl) and the mass spectrum displayed the expected molecular ion peak at m/z 208.1100. In the nmr spectrum the aromatic hydrogen atoms appeared as a multiplet at δ 7.34 whereas the ethyl ester displayed a triplet at δ 1.22 and a quartet at δ 4.15, each with a coupling constant of 7 Hz. Two broad doublets were observed at δ 2.93 and 3.72. The former was due to the benzylic hydrogens and the latter to the methylene group bearing the hydroxyl group. A broad singlet at δ 2.22 and a multiplet at δ 2.63 could be attributed to the hydroxyl group and the methine proton respectively.

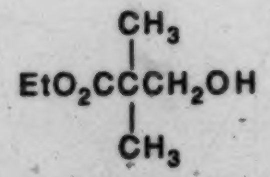
The procedure for selective reduction proved to be general. A total of twelve compounds were examined. The results are compiled in Table II. In all the cases studied, the thiolmalonate was readily reduced with Raney nickel under virtually neutral conditions to give the corresponding β-hydroxypropionate in greater than 79% yield.

Several observations are noteworthy. As expected, the rate of reaction is dependent on the reactivity of the Raney nickel used. When the freshly prepared Raney nickel was applied, the reaction was complete within 8 h even with highly hindered thiolmalonates such as **58**, **59** and **60** (Table II, Entries 10-12). On the other hand, when Raney nickel was stored in ethanol over a period of time prior to use, the reaction was found to be rather slow. In several cases the starting material was not completely consumed even over an extended reaction time. Although the reaction could be forced into completion by introduction of an additional amount of Raney nickel, the yield of product was generally inferior. Thus, it is desirable to carry out the reaction with freshly prepared Raney nickel.

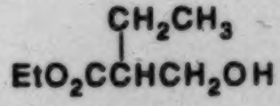
For Raney nickel desulfurization in general, extensive washing of Raney nickel residue is essential in order to obtain a high yield of the product. In the present case, as in many other cases, ethanol was found to be a highly effective solvent for washing. Furthermore, while products with high molecular weight could be efficiently purified by bulb-to-bulb distillation, the purification of the more volatile β-hydroxypropionates such as **69**, **70** and **72** (Table II, Entries 2, 3 and 5) was


$\mathrm{EtO_2C\overset{CH_3}{C}HCH_2OH}$

69


$\mathrm{EtO_2C\underset{CH_3}{\overset{CH_3}{C}}CH_2OH}$

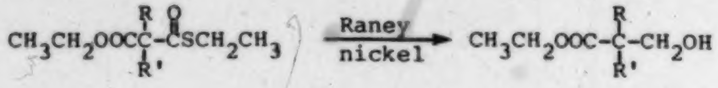
70


$\mathrm{EtO_2C\overset{CH_2CH_3}{C}HCH_2OH}$

72

best carried out using flash chromatography in order to avoid substantial loss of material.

Table II. Selective Reduction of Alkylation Products to β-Hydroxypropionates.



$$CH_3CH_2OOC\overset{R}{\underset{R'}{C}}-\overset{O}{\overset{\|}{C}}SCH_2CH_3 \xrightarrow[\text{nickel}]{\text{Raney}} CH_3CH_2OOC-\overset{R}{\underset{R'}{C}}-CH_2OH$$

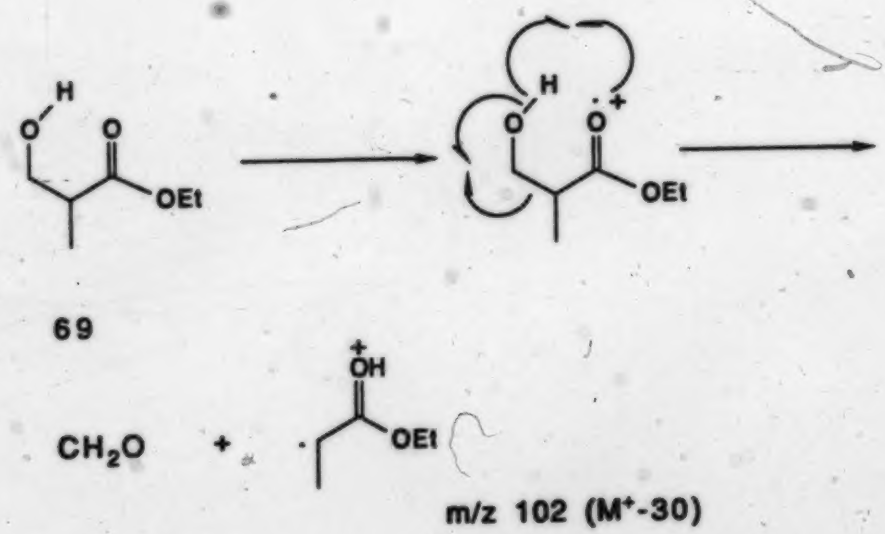
Entry	Substrate	Time (h)	Product	% Yield
1	R=PhCH$_2$, R'=H **49**	4	R=PhCH$_2$, R'=H **66**	93
2	R=CH$_3$, R'=H **47**	4	R=CH$_3$, R'=H **69**	95
3	R=R'=CH$_3$ **48**	4	R=R'=CH$_3$ **70**	
4	R=CH$_3$O$\overset{O}{\overset{\|}{C}}CH_2CH_2$, R'=H **51**	4	R=CH$_3$O$\overset{O}{\overset{\|}{C}}CH_2CH_2$, R'=H **71**	85
5	R=CH$_3$CH$_2$, R'=H **53**	4	R=CH$_3$CH$_2$, R'=H **72**	79
6	R=CH$_3$CH$_2$CH$_2$, R'=H **54**	4	R=CH$_3$CH$_2$CH$_2$, R'=H **73**	86
7	R=(CH$_3$)$_2$CH, R'=H **55**	4	R=(CH$_3$)$_2$CH, R'=H **74**	98
8	R=CH$_3$(CH$_2$)$_7$, R'=H **56**	6	R=CH$_3$(CH$_2$)$_7$, R'=H **75**	98

continued...

Table II (continued):

Entry	Substrate	Time (h)	Product	% Yield
9	$R=R'=CH_3CH_2$ **57**	4	$R=R'=CH_3CH_2$ **76**	98
10	$R=R'=CH_3CH_2CH_2$ **58**	6	$R=R'=CH_3CH_2CH_2$ **77**	95
11	$R=R'=CH_3(CH_2)_3$ **59**	8	$R=R'=CH_3(CH_2)_3$ **78**	91
12	R, $R'=(CH_2)_5$ **60**	6	R, $R'=(CH_2)_5$ **79**	96

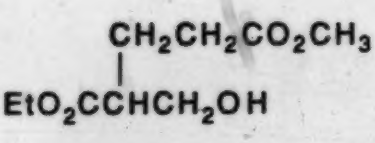
It is also worth pointing out that a large number of β-hydroxypropionates did not show molecular ion peaks in the mass spectra. Instead, a predominant fragment at M^+-30 corresponding to the loss of a CH_2O unit was observed. For example, compound **69** (Table II, Entry 2) displayed an intense fragment at m/z 102.0686 instead of a molecular ion peak (expected at m/z 132.0874). The loss of a CH_2O unit could be readily rationalized by invoking a McLafferty rearrangement[56] as shown below with compound **69**.



3. Transformation of β-hydroxypropionates to acrylate derivatives

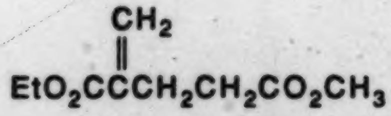
Two methods were successfully studied for the dehydration of β-hydroxypropionates to give the corresponding acrylates. These are illustrated below with specific examples.

Indirectly, compound **71** was mesylated with an excess of methanesulfonyl chloride and triethylamine in dichloromethane at room temperature for 6 h. The crude product, without purification, was subjected to treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene in refluxing benzene for 5 h. The acrylate **80** thus obtained in 76% yield displayed, in the ir spectrum, two ester absorption bands at 1740 and 1718 cm^{-1}, as well as a double bond absorption at 1636 cm^{-1}. In the nmr spectrum, the methyl ester showed a singlet at δ 3.68 and the ethyl ester a pair of mutually coupled signals at δ 1.25 and 4.20, each with a coupling constant of 7 Hz. The ethylene unit appeared as a pair of triplets (J = 7 Hz) at δ 2.38 and 2.28. The



$EtO_2CCH(CH_2CH_2CO_2CH_3)CH_2OH$

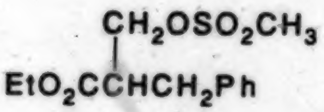
71



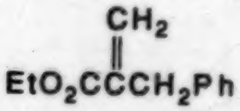
$EtO_2CC(=CH_2)CH_2CH_2CO_2CH_3$

80

latter signal was broadened due to allylic coupling with vinyl hydrogens which appeared at δ 5.60, a doublet with a coupling constant of 1 Hz, and δ 6.20, a broad singlet. The structural assignment was confirmed by the mass spectrum exhibiting a molecular ion peak at 186.0892. As a further example, the dehydration of compound **66** was also done via the intermediacy of mesylate **81** to give compound **82** in 96% yield. This acrylate derivative showed,


$\mathrm{EtO_2C\overset{CH_2OSO_2CH_3}{\overset{|}{C}}HCH_2Ph}$

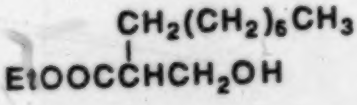
81


$\mathrm{EtO_2C\overset{CH_2}{\overset{\|}{C}}CH_2Ph}$

82

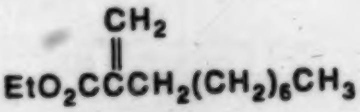
in the ir spectrum, absorption bands at 3040-3100 (aromatic), 1718 (ester carbonyl), 1636 (C=C), 1605 cm^{-1} and 1586 (phenyl), 745 and 701 cm^{-1} (monosubstituted benzene). In the nmr spectrum, the ethyl ester showed signals at δ 1.26 and 4.18, each with a coupling constant of 7 Hz. A broad singlet at δ 3.64 was due to benzylic protons. Two doublets, one at δ 5.45 (J = 1 Hz) and the other at δ 6.22 (J = 1 Hz) were attributed to the vinylic protons. The aromatic protons appeared as a multiplet at δ 7.27. The structural assignment was confirmed by the mass spectrum which showed a molecular ion peak at m/z 190.0901.

In 1971, Alexandre and Rousessac[57] reported a facile method for the dehydration of β-hydroxy ketones using dicyclohexylcarbodiimide in the presence of cuprous chloride. This method proved to be especially useful in the preparation of unstable conjugated enones and has been extended to the dehydration of β-hydroxypropionitriles.[37] Application of this method to compound 75 gave rise to a 92% yield of compound 83 which showed



$EtOOC\overset{\overset{CH_2(CH_2)_6CH_3}{|}}{C}HCH_2OH$

75



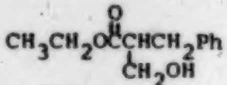
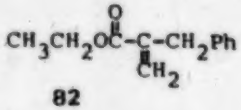
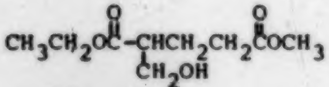
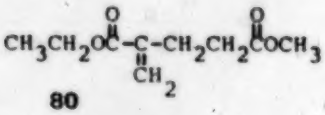
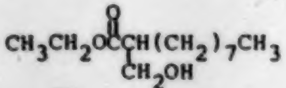
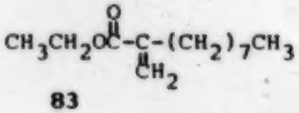
$EtO_2C\overset{\overset{CH_2}{\|}}{C}CH_2(CH_2)_6CH_3$

83

absorption bands at 1719 (ester carbonyl) and 1625 cm^{-1} (C=C) in the ir spectrum, and a molecular ion peak at m/z 212.1778 in the mass spectrum. The presence of α-substituted ethyl acrylate unit was evident from the nmr spectrum which showed a 3H triplet (J = 7 Hz) at δ 1.25, a 2H quartet (J = 7 Hz) at 4.20, a 1H doublet of doublets (J = J' = 1.5 Hz) at δ 5.50 and a 1H doublet (J = 1.5 Hz) at δ 6.12. The above results are further outlined in Table III.

In conclusion, a convenient method for the preparation of β-hydroxypropionate and acrylate derivatives has been developed using O,S-diethyl thiolmalonate 23 as a

Table III. Dehydration of Ethyl β-Hydroxypropionates.

Entry	Alcohol	Reagent (Equiv.)	Ethyl Acrylate	% Yield
1	 $CH_3CH_2O\overset{O}{\overset{\|}{C}}\underset{CH_2OH}{C}HCH_2Ph$ **66**	(i) MsCl[a] (3.0) Et_3N (5.0) (ii) DBU, C_6H_6[b]	 $CH_3CH_2O\overset{O}{\overset{\|}{C}}-\underset{\overset{\|}{CH_2}}{C}-CH_2Ph$ **82**	96
2	 $CH_3CH_2O\overset{O}{\overset{\|}{C}}-\underset{CH_2OH}{C}HCH_2CH_2\overset{O}{\overset{\|}{C}}OCH_3$ **71**	(i) MsCl[a] (3.0) Et_3N (5.0) (ii) DBU, C_6H_6[b]	 $CH_3CH_2O\overset{O}{\overset{\|}{C}}-\underset{\overset{\|}{CH_2}}{C}-CH_2CH_2\overset{O}{\overset{\|}{C}}OCH_3$ **80**	76
3	 $CH_3CH_2O\overset{O}{\overset{\|}{C}}\underset{CH_2OH}{C}H(CH_2)_7CH_3$ **75**	DCC[c] (2.0)	 $CH_3CH_2O\overset{O}{\overset{\|}{C}}-\underset{\overset{\|}{CH_2}}{C}-(CH_2)_7CH_3$ **83**	92

[a] Dichloromethane was used as solvent.

[b] At reflux.

[c] The reaction was performed in refluxing ether in the presence of a trace amount of copper(I) chloride.

common starting material. The method is operationally simple and apparently general. All the transformations could be done under rather mild conditions which would not affect most of the other functionalities frequently encountered in organic synthesis.

EXPERIMENTAL

General

Elemental analyses were performed by the microanalytical laboratory of this department. Infrared (ir) spectra were recorded on Perkin-Elmer model 457 or Nicolet 7-199 FT-IR spectrophotometer. Unless otherwise stated, ir samples were run as thin films. Proton nuclear magnetic resonance (nmr) spectra were recorded on a Bruker WH-200, WH-400, or AM-300 spectrometer and, except where stated, were obtained on solutions in deuterochloroform using tetramethylsilane as internal reference.

The following abbreviations were used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and br = broad. Mass spectra (ms) were recorded on Kratos A.E.I. model MS-50 or MS-12 mass spectrometers. Whenever possible the progress of reaction was monitored by thin layer chromatography using one or more of the following for visualization: UV absorption by fluorescence quenching; I_2-staining; (1:1) methanol/H_2SO_4 spray with charring; acidic solution of vanillin in methanol; aq. solution of 3% phosphomolybolic acid and 0.5% ceric sulfate in 3% H_2SO_4. Concentration of solvent systems used in column chromatography are given by volumes, e.g.

10% ether in petroleum ether, means 10 parts of ether by volume to 90 parts of petrolem ether by volume. One or more of the following solvent systems was used: EtOAc/petroleum ether (most generally satisfactory);[58] CH_2Cl_2/petroleum ether; EtOAc/CH_2Cl_2; and ether/petroleum ether (for less polar mixtures). All spray reagents were prepared and used as described by Kreibs _et al_.[59] The flash chromatography was executed according to Still _et al_.[54] and "Dry-column" flash chromatography according to Harwood.[60] The reactions were done under a positive pressure of dry argon.

Materials

Ether and benzene used for reactions were freshly distilled from lithium aluminium hydride. Tetrahydrofuran and 1,2-dimethoxyethane were distilled from sodium and benzophenone. Toluene and ethyl acetate were distilled from calcium hydride. Absolute ethanol was obtained by distilling 95% ethanol over magnesium turnings in the presence of a few crystals of iodine. Argon was passed through a purification train of Fieser's solution,[61] concentrated sulfuric acid and potassium hydroxide pellets. The Fieser's solution was prepared by adding sodium dithionate to a cold solution of sodium hydroxide followed by the sodium salt of anthraquinone B sulfonic acid. Merck 60GF$_{254}$ silica gel was used for thin layer chromatography. Silica gel, type 60, 230-400 mesh, was used for flash chromatography and type 60, 70-230 mesh was used for gravity chromatography. Unless otherwise stated, anhydrous magnesium sulfate was used for drying organic solutions. Solutions were concentrated under reduced pressure. Commercially available sodium hydride (80% dispersion in oil) was washed several times with petroleum ether before use. Commercially available iodomethane, iodoethane, 1-iodopropane, 2-iodopropane, 1-iodobutane, benzyl bromide, methyl β-bromopropionate, 1,5-diiodopentane and 1-bromooctane were used without further purification.

W-2 Raney nickel

A solution of sodium hydroxide (190 g) in distilled water (750 mL) was cooled in an ice-bath. Nickel-aluminium alloy (150 g) was added in small portions with stirring. During the addition, the temperature of the mixture was not allowed to rise above 25°C. After the addition, the mixture was allowed to stand at room temperature until the evolution of hydrogen stopped. The mixture was heated on a steam bath with stirring for 12 h. The solvent was decanted and the residue washed thoroughly with distilled water until neutral. The residue was further washed with absolute ethanol (3 x 250 mL) and stored under ethanol.

O,S-Diethyl thiolmalonate (23)

A solution of ethanethiol (3.03 mL, 41 mmol) in tetrahydrofuran (10 mL) was added dropwise to a solution of ethyl malonyl chloride (4.74 mL, 31 mmol) in tetrahydrofuran (30 mL) at 0°C under an argon atmosphere. The reaction mixture was allowed to stand at room temperature for 24 h. Most of the solvent was evaporated and the residue distilled at 60°C/1 torr. The distillate was further purified by flash chromatography on silica gel using 20% ether in petroleum ether as eluent to afford thiolmalonate **23** (5.34 g, 96% yield): ir 1742 (ester carbonyl) and 1688 cm^{-1} (thiolester carbonyl); nmr δ 1.28 (t, 3H, J = 8 Hz, $-SCH_2\underline{CH_3}$), 1.29 (t, 3H, J = 8 Hz, $-OCH_2\underline{CH_3}$), 2.95 (q, 2H, J = 8 Hz, $-S\underline{CH_2}CH_3$), 3.57 (s, 2H, $-COCH_2CO-$) and 4.20 (q, 2H, J = 8 Hz, $-O\underline{CH_2}CH_3$); ms M$^+$ 176.0509 (calcd. for $C_7H_{12}O_3S$: 176.0507).

Addition of iodomethane to O,S-diethyl thiolmalonate (23)

A solution of O,S-diethyl thiolmalonate (270 mg, 1.54 mmol) in tetrahydrofuran (15 mL) was added dropwise to sodium hydride (50.6 mg, 1.69 mmol) in tetrahydrofuran (10 mL) at 0°C. The solution was stirred under argon for

10 min. A solution of iodomethane (0.095 mL, 1.53 mmol) in tetrahydrofuran (1.0 mL) was then added and the mixture was stirred for 3 h. The reaction was quenched with ice-cold 1 N aqueous hydrochloric acid solution and extracted with dichloromethane (3 x 20 mL). The extracts were combined, washed with saturated sodium chloride solution, dried, filtered and concentrated. Flash chromatography of the residue on silica gel eluting with 20% ether in petroleum ether gave the following products. Monoalkylated product **47** as a colourless oil (233 mg, 80% yield): ir 1749 (ester carbonyl) and 1688 cm^{-1} (thiolester carbonyl); nmr δ 1.25 (t, 3H, J = 8 Hz, $-SCH_2C\underline{H_3}$), δ 1.26 (t, 3H, J = 8 Hz, $-OCH_2C\underline{H_3}$) 1.50 (d, 3H, J = 7.5 Hz, $-\overset{|}{C}HC\underline{H_3}$), 2.96 (q, 2H, J = 8 Hz, $-SC\underline{H_2}CH_3$), 3.65 (q, 1H, J = 7.5 Hz, $-\overset{|}{C}\underline{H}CH_3$), and 4.20 (q, 2H, J = 8 Hz, $-OC\underline{H_2}CH_3$); ms M^+ 190.0657 (calcd. for $C_8H_{14}O_3S$: 190.0663). Anal. Calcd. for $C_8H_{14}O_3S$: C 50.53, H 7.37, S 16.84; Found: C 50.48, H 7.77, S 16.73. Dialkylated product **48** as a colourless oil (34.70 mg, 11% yield): ir 1739 (ester carbonyl) and 1682 cm^{-1} (thiolester carbonyl); nmr δ 1.25 (t, 3H, J = 7 Hz, $-SCH_2C\underline{H_3}$), 1.26 (t, 3H, J = 7 Hz, $-OCH_2C\underline{H_3}$), 1.48 (s, 6H, $-\overset{|}{C}(CH_3)_2$), 2.90 (q, 2H, J = 7 Hz, $-SC\underline{H_2}CH_3$) and 4.18 (q, 2H, J = 7 Hz, $-OC\underline{H_2}CH_3$); ms M^+ 204.0818 (calcd. for $C_9H_{16}O_3S$: 204.0820). Anal. Calcd.

for $C_9H_{16}O_3S$: C 52.94, H 7.89, S 15.69; Found: C 52.95, H 7.92, S 15.68.

Dimethylation of **23**

A solution of O,S-diethyl thiolmalonate (901 mg, 5.46 mmol) in tetrahydrofuran (10 mL) was added dropwise to sodium hydride (491 mg, 16.37 mmol) in tetrahydrofuran (10 mL) at 10°C. The solution was stirred under an argon atmosphere for 20 min. Then a solution of iodomethane (0.714 mL, 11.47 mmol) in tetrahydrofuran (2 mL) was added and the mixture was stirred at room temperature for 4 h. The reaction mixture was quenched with ice-cold 1 N hydrochloric acid solution and then extracted with dichloromethane (3 x 25 mL). The extracts were combined, washed with saturated sodium chloride solution, dried, filtered and concentrated. The residue was purified by flash chromatography on silica gel, eluting with 10% ether in petroleum ether to afford adduct **48** (1.08 g, 97% yield). The spectral results (ir, ^{1}H nmr and ms) were identical to those already obtained (vide supra).

Alkylation of **23** with benzyl bromide

A solution of thiolester **23** (3.335 g, 18.95 mmol) in dry tetrahydrofuran (10 mL) was added slowly to a suspension of sodium hydride (770 mg, 25.67 mmol) in tetrahydrofuran (25 mL) at 0°C. The solution was stirred under an argon atmosphere for 20 min. A solution of benzyl bromide (2.48 mL, 20.85 mmol) in tetrahydrofuran (5 mL) was added. The mixture was stirred at room temperature for 4 h. The reaction was quenched with ice-cold 1 N hydrochloric acid solution then extracted with dichloromethane (4 x 25 mL). The extracts were combined, washed with saturated sodium chloride solution, dried, filtered and concentrated. The residue was chromatographed on silica gel, eluting with 20% ether in petroleum ether to afford pure adduct **49** (3.607 g, 72%): ir 1742 (ester carbonyl), 1684 cm^{-1} (thiolester carbonyl), 1604 and 1584 cm^{-1} (aromatic C=C); nmr δ 1.20 (t, 3H, J = 7 Hz, $-SCH_2C\underline{H_3}$), 1.22 (t, 3H, J = 7 Hz, $-OCH_2C\underline{H_3}$), 2.90 (q, 2H, J = 7 Hz, $-SC\underline{H_2}CH_3$), 3.22, 3.25 (both d, 1H each, J = 8 Hz each, $-CH_2Ph$), 3.84 (t, 1H, J = 8 Hz, $-COC\underline{H}CO-$), 4.15 (q, 2H, J = 7 Hz, $-OC\underline{H_2}CH_3$) and 7.22 (m, 5H, aromatic protons); ms M^+ 266.0975 (calcd. for $C_{14}H_{18}O_3S$: 266.0977). Anal. Calcd. for $C_{14}H_{18}O_3S$: C 63.13, H 6.80, S 12.02; Found: C 63.07, H 6.80, S 11.83. Further elution with the same solvent system afforded the dibenzyl adduct **50** (166 mg, 2% yield): ir 1741 (ester carbonyl), 1684 (thiolester carbonyl), 1604 and 1586 cm^{-1} (phenyl); nmr δ 1.22 (t, 3H, J = 7 Hz, $-SCH_2C\underline{H_3}$), 1.23 (t, 3H, J = 7 Hz, $-OCH_2C\underline{H_3}$), 2.92 (q, 2H, J = 7 Hz, $-SC\underline{H_2}CH_3$), 3.34 (s, 4H, 2 x $-C\underline{H_2}Ph$), 4.16 (q, 2H, J = 7 Hz, $-OC\underline{H_2}CH_3$) and 7.23

(m, 10H, aromatic protons); ms M^+ 356.1454 (calcd. for $C_{21}H_{24}O_3S$: 356.1446).

Further elution with 20% ether in petroleum ether afforded unreacted **23** (523 mg, 16% recovery).

Addition of methyl 3-bromopropionate to O,S-diethyl thiolmalonate (**23**)

A solution of thiolester **23** (1.89 g, 10.45 mmol) in dry tetrahydrofuran (10 mL) was added slowly to a suspension of sodium hydride (424 mg, 14.13 mmol) in tetrahydrofuran (15 mL) at 0°C. The solution was stirred under an argon atmosphere for 10 min. A solution of methyl 3-bromopropionate (1.26 mL, 11.54 mmol) in tetrahydrofuran (5 mL) was added. The mixture was stirred at room temperature for 12 h. The reaction mixture was quenched with ice-cold 1 N hydrochloric acid solution then extracted with dichloromethane (3 x 25 mL). The extracts were combined, washed with saturated sodium chloride solution, dried, filtered and concentrated. The residue was chromatographed on silica gel, eluting with 20% ether in petroleum ether to afford pure adduct **51** (1.63 g, 66% yield): ir 1741 (ester carbonyl) and 1683 cm^{-1} (thiolester carbonyl); nmr δ 1.25 (t, 3H, J = 7 Hz, $-SCH_2C\underline{H_3}$), 1.26 (t, 3H, J = 7 Hz, $-OCH_2C\underline{H_3}$), 2.24 (q, 2H, J = 7 Hz, $-\overset{|}{C}HC\underline{H_2}-$), 2.38 (t, 2H, J = 7 Hz, $-CH_2C\underline{H}_2CO-$), 2.92 (q, 2H, J = 7 Hz, $-SC\underline{H}_2CH_3$), 3.65 (t, 1H, J = 7 Hz, $-CO\overset{|}{C}HCO-$), 3.68 (s, 3H, $-OC\underline{H}_3$) and 4.20 (q, 2H, J = 7 Hz, $-OC\underline{H}_2CH_3$); ms m/z 231.0686 (M^+-31; calcd. for $C_{10}H_{15}O_4S$: 231.0691) and 201.0758 (M^+-61, calcd. for $C_9H_{13}O_5$: 201.0762); Anal. Calcd. for $C_{11}H_{18}O_5S$: C 50.37, H 6.92, S 12.21; Found: C 50.24, H 7.04, S 11.98.

Further elution with the same solvent system afforded the dialkylated compound **52** (301 mg, 8% yield): ir 1740 (ester carbonyl) and 1684 cm^{-1} (thiolester), nmr δ 1.26 (t, 6H, J = 7 Hz, $-SCH_2C\underline{H}_3$, $-OCH_2C\underline{H}_3$); 1.84 (t, 4H, 7 Hz, 2 x $-C\underline{H}_2CH_2CO-$), 2.40 (t, 4H, J = 7 Hz, 2 x $-CH_2C\underline{H}_2CO-$), 2.92 (q, 2H, J = 7 Hz, $-SC\underline{H}_2CH_3$), 3.68 (s, 6H, 2 x $-OCH_3$), 4.20 (q, 2H, J = 7 Hz, $-OC\underline{H}_2CH_3$), ms m/z 317.1063 (M^+-31, calcd. for $C_{14}H_{21}O_6S$: 317.1059), and 287.1136 (M^+-61, calcd. for $C_{13}H_{19}O_7$: 287.1131). Further elution using the same solvent system afforded the unreacted thiolester **23** (221 mg, 12% recovery).

Addition of iodoethane to 23

A solution of thiolmalonate **23** (903 mg, 5.13 mmol) in tetrahydrofuran (5 mL) was added dropwise to a suspension of sodium hydride (184 mg, 6.12 mmol) in tetrahydrofuran (10 mL) at 0°C. The reaction mixture was stirred under an argon atmosphere for 10 min. The solution of iodoethane

(0.451 mL, 5.64 mmol) in tetrahydrofuran (5 mL) was added and the mixture stirred at room temperature for 14 h. The reaction mixture was quenched with ice cold 1 N aqueous hydrochloric acid solution and extracted with dichloromethane (2 x 20 mL). The extracts were combined, washed with saturated sodium chloride solution, dried, filtered and concentrated. Chromatography of the residue on the silica gel, eluting with 10% ether in petroleum ether gave adduct **53** (942 mg, 90% yield): ir 1742 cm^{-1} (ester carbonyl) and 1648 cm^{-1} (thiolester carbonyl); nmr δ 0.96 (t, 3H, J = 7.5 Hz, $-CH_2C\underline{H}_3$), 1.25 (t, 3H, J = 8 Hz, $-SCH_2C\underline{H}_3$), 1.26 (t, 3H, J = 8 Hz, $-OCH_2C\underline{H}_3$), 1.98 (m, 2H, $-CH_2C\underline{H}_3$), 2.92 (q, 2H, J = 8 Hz, $-SC\underline{H}_2CH_3$), 3.46 (t, 1H, J = 8 Hz, $-CO\overset{|}{C}HCO-$) and 4.20 (q, 2H, J = 8 Hz, $-OC\underline{H}_2CH_3$); ms M^+ 204.0824 (calcd. for $C_9H_{16}O_3S$: 204.0820); Anal. Calcd. for $C_9H_{16}O_3S$: C 52.92, H 7.89, S 15.68; Found: C 52.89, H 7.94, S 15.69.

Monoalkylation of **23** with 1-iodopropane

A solution of O,S-diethyl thiolmalonate (919 mg, 5.22 mmol) in dry tetrahydrofuran (10 mL) was added dropwise to a suspension of sodium hydride (188 mg, 6.26 mmol) in tetrahydrofuran (10 mL) at 0°C. The solution was stirred under an argon atmosphere until the evolution of hydrogen gas stopped. A solution of 1-iodopropane (0.560 mL, 5.74

mmol) in tetrahydrofuran (5 mL) was added and the mixture was stirred for 8 h at room temperature. The reaction mixture was quenched with ice-cold 1 N hydrochloric acid solution and extracted with dichloromethane (3 x 15 mL). The extracts were combined, washed with saturated sodium chloride solution, dried, filtered and concentrated. The crude material was chromatographed on silica gel, eluting with 10% ether in petroleum ether to afford pure adduct **54** (933 mg, 82% yield): ir 1739 (ester carbonyl) and 1685 cm^{-1} (thiolester carbonyl); nmr δ 0.92 (t, 3H, J = 8 Hz, $-(CH_2)_2C\underline{H_3}$), 1.25 (t, 3H, J = 8 Hz, $-SCH_2C\underline{H_3}$), 1.26 (t, 3H, J = 8 Hz, $-OCH_2C\underline{H_3}$), 1.35 (m, 2H, J = 8 Hz, $-CH_2C\underline{H_2}CH_3$), 1.90 (m, 2H, $-C\underline{H_2}CH_2CH_3$), 2.92 (q, 2H, J = 8 Hz, $-SC\underline{H_2}CH_3$), 3.54 (t, 1H, J = 7 Hz, $-COC\underline{H}CO-$) and 4.20 (q, 2H, J = 8 Hz, $-OC\underline{H_2}CH_3$); ms M$^+$ 218.0974 (calcd. for $C_{10}H_{18}O_2S$: 218.0976). Anal. Calcd. for $C_{10}H_{18}O_3S$: C 55.02, H 8.25, S 14.62; Found: C 54.82, H 8.22, S 14.58.

Further elution afforded the unreacted **23** (82 mg, 9% recovery).

Addition of 2-iodopropane to 23

A solution of thiolester **23** (793 mg, 4.51 mmol) in dry tetrahydrofuran (10 mL) was added dropwise to a suspension of sodium hydride (162 mg, 5.43 mmol) in tetrahydrofuran (10 mL) at 0°C. The solution was stirred under an argon atmosphere until the evolution of hydrogen gas stopped. A solution of 2-iodopropane (0.493 mL, 4.96 mmol) in tetrahydrofuran (5 mL) was added. The mixture was heated at 50°C for 8 h. The reaction mixture was cooled to room temperature and then quenched with ice-cold hydrochloric acid solution (1 N) followed by extraction with dichloromethane (3 x 25 mL). The extracts were combined, washed with saturated sodium chloride solution, dried, filtered and concentrated. The residue was chromatographed on silica gel, eluting with 10% ether in petroleum ether to afford pure alkylation adduct 55 (615 mg, 63% yield): ir 1743 (ester carbonyl) and 1686 cm^{-1} (thiol ester carbonyl); nmr δ 0.96 (d, 3H, J = 7 Hz, $-CH(C\underline{H}_3)CH_3$), 0.98 (d, 3H, J = 7 Hz, $-CH(CH_3)C\underline{H}_3$), 1.25 (t, 3H, J = 7 Hz, $-SCH_2C\underline{H}_3$), 1.26 (t, 3H, J = 7 Hz, $-OCH_2C\underline{H}_3$), 2.48 (m, 1H, $-C\underline{H}(CH_3)_2$), 2.92 (q, 2H, J = 7 Hz, $-SC\underline{H}_2CH_3$), 3.28 (d, 1H, J = 9 Hz, $-CO\overset{|}{C}HCO$) and 4.20 (q, 2H, J = 7 Hz, $-OC\underline{H}_2CH_3$); ms M^+ 218.0978 (calcd. for $C_{10}H_{18}O_3S$: 218.0977). Anal. Calcd. for $C_{10}H_{18}O_3S$: C 55.0, H 8.30, S 14.69; Found: C 54.95, H 8.29, S 14.44.

Further elution with the same solvent system afforded the unreacted thiolester 23 (214 mg, 26% recovery).

Addition of 1-bromooctane to O,S-diethyl thiolmalonate (23)

A. Without sodium iodide

A solution of thiolester **23** (2.40 g, 13.64 mmol) in freshly distilled tetrahydrofuran (15 mL) was added slowly to a suspension of sodium hydride (522 mg, 18.40 mmol) in tetrahydrofuran (15 mL) at 0°C. The solution was stirred under an argon atmosphere for 20 min. A solution of 1-bromooctane (2.59 mL, 14.99 mmol) in tetrahydrofuran (5 mL) was added. The mixture was heated at reflux for 24 h. The mixture was cooled, quenched with ice-cold 1 N hydrochloric acid solution and extracted with dichloromethane (4 x 25 mL). The extracts were combined, washed with saturated sodium chloride solution, dried, filtered and concentrated. The residue was chromatographed on silica gel, eluting with 10% ether in petroleum ether to afford pure adduct **56** (2.17 g, 55% yield): ir 1744 (ester carbonyl) and 1689 cm^{-1} (thiolester carbonyl); nmr δ 0.87 (t, 3H, J = 7 Hz, $-(CH_2)_7C\underline{H_3}$), 1.28 (m, 18H, $-OCH_2C\underline{H_3}$, $-SCH_2C\underline{H_3}$, $-(C\underline{H_2})_6CH_3$), 1.90 (q, 2H, J = 7 Hz, $-\overset{|}{C}HC\underline{H_2}-$), 2.92 (q, 2H, J = 7 Hz, $-SC\underline{H_2}CH_3$), 3.54 (t, 1H, J = 7 Hz, $-CO\overset{|}{C}\underline{H}CO-$), 4.20 (q, 2H, J = 7 Hz, $-OC\underline{H_2}CH_3$); ms M^+ 288.1760 (calcd. for $C_{15}H_{28}O_3S$: 288.1759). *Anal*. Calcd. $C_{15}H_{28}O_3S$: C 62.46, H 9.78, S 11.11; Found: C 62.45, H 9.72, S 11.10.

Further elution using the same solvent system afforded unconsumed O,S-diethyl thiolmalonate (579 mg, 24% recovery).

B. With sodium iodide

A solution of O,S-diethyl thiolmalonate (458 mg, 2.60 mmol) in freshly distilled tetrahydrofuran (5 mL) was added slowly to a suspension of sodium hydride (101 mg, 3.36 mmol) in tetrahydrofuran (10 mL) at 0°C. The solution was stirred under an argon atmosphere for 10 min. A solution of 1-bromooctane (0.517 mL, 2.98 mmol) in tetrahydrofuran (5 mL) was added followed by a catalytic amount of sodium iodide (39.3 mg, 0.26 mmol). The mixture was heated at reflux for 24 h. Usual work-up and purification as in method A afforded ester **56** (525 mg, 70% yield) and unreacted **23** (86 mg, 19% recovery). The ir, ^{1}H nmr and mass spectra were identical to those reported previously (vide supra).

Dialkylation of O,S-diethyl thiolmalonate (23) with iodoethane

A solution of O,S-diethyl thiolmalonate (844 mg, 4.80 mmol) in dry tetrahydrofuran (10 mL) was added dropwise to a suspension of sodium hydride (460 mg, 15.33 mmol) in tetrahydrofuran (10 mL) at 0°C. The solution was stirred under an argon atmosphere until the evolution of hydrogen stopped. Then a solution of iodoethane (1.23 mL, 15.38 mmol) in tetrahydrofuran (5 mL) was added and stirring was continued at room temperature for 6 h. The reaction mixture was quenched with ice-cold 1 N hydrochloric acid solution, extracted with dichloromethane (3 x 25 mL) and then the extracts washed with saturated sodium chloride solution. The combined extracts were dried, filtered and concentrated. Chromatography of the residue on silica gel eluting with 10% ether in petroleum ether gave compound **57** (917 mg, 82% yield): ir 1739 (ester carbonyl) and 1685 cm^{-1} (thiolester carbonyl); nmr δ 0.93 (t, 6 H, J = 8 Hz, 2 x $-CH_2C\underline{H_3}$), 1.26 (t, 3H, J = 8 Hz, $-SCH_2C\underline{H_3}$), 1.26 (t, 3H, J = 8 Hz, $-OCH_2C\underline{H_3}$), 2.02 (q, 4H, J = 8 Hz, 2 x $-C\underline{H_2}CH_3$), 2.90 (q, 2H, J = 8 Hz, $-SC\underline{H_2}CH_3$) and 4.20 (q, 2H, J = 8 Hz, $-OC\underline{H_2}CH_3$); ms M^+ 232.1141 (calcd. for $C_{11}H_{20}O_3S$: 232.1133). Anal. Calcd. for $C_{11}H_{20}O_3S$: C 56.90, H 8.68, S 13.80; Found: C 57.05, H 8.71, S 13.45.

Dialkylation of O,S-diethyl thiolmalonate (**23**) with 1-iodopropane

A solution of O,S-diethyl thiolmalonate (745 mg, 4.23 mmol) in dry tetrahydrofuran (10 mL) was added dropwise to a suspension of sodium hydride (406 mg, 13.53 mmol) in tetrahydrofuran (10 mL) at 0°C. The solution was stirred under an argon atmosphere for 20 min. Then a solution of 1-iodopropane (1.03 mL, 10.56 mmol) was added and stirring was continued at room temperature for 12 h. The reaction mixture was quenched with ice-cold 1 N hydrochloric acid solution and then extracted with dichloromethane (3 x 25 mL). The extracts were combined, washed with saturated sodium chloride solution, dried, filtered and concentrated. The crude material was chromatographed on silica gel, eluting with 10% ether in petroleum ether to afford pure adduct **58** (989 mg, 90% yield): ir 1739 (ester carbonyl) and 1685 cm^{-1} (thiolester carbonyl); nmr δ 0.92 (t, 6H, J = 7 Hz, 2 x $-(CH_2)_2\underline{CH_3}$), 1.21 (t, 3H, J = 7 Hz, $-SCH_2\underline{CH_3}$), 1.22 (t, 3H, J = 7 Hz, $-OCH_2\underline{CH_3}$), 1.29 (m, 4H, 2 x $-CH_2\underline{CH_2}CH_3$), 1.92 (t, 4H, J = 7 Hz, 2 x $-\underline{CH_2}CH_2CH_3$), 2.90 (q, 2H, J = 7 Hz, $-S\underline{CH_2}CH_3$) and 4.18 (q, 2H, J = 7 Hz, $-O\underline{CH_2}CH_3$); ms M^+ 260.1444 (calcd. for $C_{13}H_{24}O_3S$: 260.1446); Anal. Calcd. for $C_{13}H_{24}O_3S$: C 60.0, H 9.23, S 12.31; Found: C 59.89, H 9.16, S 12.07.

Dialkylation of **23** with 1-iodobutane

A solution of O,S-diethyl thiolmalonate (560 mg 3.18 mmol) in dry tetrahydrofuran (5 mL) was added dropwise to a suspension of sodium hydride (305 mg, 10.17 mmol) in tetrahydrofuran (10 mL) at 0°C. The solution was stirred under a argon atmosphere until evolution of hydrogen stopped. A solution of 1-iodobutane (0.905 mL, 7.95 mmol) in tetrahydrofuran (5 mL) was added. The mixture was stirred at room temperature for 24 h. The reaction mixture was quenched with ice-cold 1 N hydrochloric acid solution then extracted with dichloromethane (3 x 25 mL). The extracts were combined, washed with saturated sodium chloride solution, dried, filtered and concentrated. The crude product was distilled under vacuum and then chromatographed on silica gel, eluting with 10% ether in petroleum ether to afford pure adduct 59 (741 mg, 81% yield): ir 1739 (ester carbonyl) and 1686 cm^{-1} (thiolester carbonyl); nmr δ 0.92 (t, 6H, J = 7 Hz, 2 x $-(CH_2)_3C\underline{H_3}$) 1.25 (m, 14H, 2 x $-CH_2(C\underline{H_2})_2CH_3$, $-OCH_2C\underline{H_3}$, $-SCH_2C\underline{H_3}$), 1.92 (t, 4 H, J = 7 Hz, 2 x $-C\underline{H_2}(CH_2)_2CH_3$), 2.90 (q, 2H, J = 7 Hz, $-SC\underline{H_2}CH_3$), 4.18 (q, 2H, J = 7 Hz, $-OC\underline{H_2}CH_3$); ms M^+ 288.1759 (calcd. for $C_{15}H_{28}O_3S$: 288.1759). Anal. Calcd. for $C_{15}H_{28}O_3S$: C 62.46, H 9.78, S 11.10; Found: C 62.37, H 9.74, S 10.91.

Alkylation of 23 with 1,5-diiodopentane

A. With 3 equiv. of NaH

A solution of thiolester 23 (985 mg, 5.61 mmol) in dry tetrahydrofuran (10 mL) was added slowly to a suspension of sodium hydride (506 mg, 16.87 mmol) in tetrahydrofuran (10 mL) at 0°C. The solution was stirred under an argon atmosphere for 20 min. A solution of 1,5-diiodopentane (1.09 mL, 7.33 mmol) in tetrahydrofuran (10 mL) was added. The mixture was stirred at room temperature for 24 h. The reaction mixture was then quenched with ice-cold 1 N hydrochloric acid solution and extracted with dichloromethane (3 x 25 mL). The extracts were combined, washed with saturated sodium chloride solution, dried, filtered and concentrated. The residue was chromatographed on silica gel, eluting with 10% ether in petroleum ether to afford ester **60** (769 mg, 56% yield): ir 1735 (ester carbonyl) and 1687 cm^{-1} (thiolester carbonyl); nmr δ 1.23 (t, 3H J = 7 Hz, $-SCH_2C\underline{H}_3$), 1.24 (t, 3H, J = 7 Hz, $-OCH_2C\underline{H}_3$), 1.48 (br, m, 6H, cyclohexyl protons), 1.90 (br, m, 2H, cyclohexyl protons), 2.15 (br, m, 2H, cyclohexyl protons), 2.88 (q, 2H, J = 7 Hz, $-SC\underline{H}_2CH_3$) and 4.22 (q, 2H, J = 7 Hz, $-OC\underline{H}_2CH_3$); ms M^+ 244.1133 (calcd. for $C_{12}H_{20}O_3S$: 244.1133). Anal. Calcd. for $C_{12}H_{20}O_3S$: C 59.02, H 8.20, S 13.14; Found: C 59.08, H 8.18, S 13.10.

Further elution using the same solvent system afforded iodo compound **61** (278 mg, 13% yield): ir 1735 (ester carbonyl) and 1644 cm^{-1} (thiolester carbonyl); nmr δ 1.23 (t, 3H, J = 7 Hz, $-SCH_2C\underline{H}_3$), J = 1.24 (t, 3H, J = 7 Hz, $-OCH_2C\underline{H}_3$), 2.90 (q, 2H, J = 7 Hz, $-SC\underline{H}_2CH_3$), 3.18 (t, 2H, J = 7 Hz, $-C\underline{H}_2I$), 3.55 (t, 1H, J = 7 Hz, -COCHCO-) and

4.20 (q, 2H, J = 7 Hz, $-OCH_2CH_3$); ms M^+ 372.0259 (calcd. for $C_{12}H_{21}O_3SI$: 372.0258). Anal. Calcd. for $C_{12}H_{21}O_3SI$: C 38.71, H 5.65, S 8.60, I 34.09; Found: C 38.43, H 5.38, S 8.51, I 33.81.

Unconsumed thiolester **23** was also recovered (194 mg, 20% recovery).

B. With 4 equiv. NaH

A solution of thiolmalonate **23** (853 mg, 4.85 mmol) in tetrahydrofuran (10 mL) was added slowly to a suspension of sodium hydride (582 mg, 19.4 mmol) in tetrahydrofuran at 0°C. The solution was stirred under an argon atmosphere for 20 min. A solution of 1,5-diiodopentane (0.792 mL, 5.33 mmol) in tetrahydrofuran (15 mL) was added. The mixture was stirred at room temperature for 30 h. Usual work up and purification as in method A afforded adduct **60** (793 mg, 67% yield) and iodo-adduct **61** (186 mg, 10% yield). Spectral results (ir, ^1H nmr and ms) were identical to those obtained by method A (vide supra). Further elution using 20% ether in petroleum ether produced the following compounds in order of chromatographic separation. The diiodo adduct **62** (123 mg, 4% yield): ir 1736 (ester carbonyl) and 1642 (thiolester carbonyl); nmr 1.22 (t, 3H, J = 7 Hz, $-SCH_2CH_3$), 1.23 (t, 3H, J = 7 Hz, $-OCH_2CH_3$), 2.92 (q, 2H, J = 7 Hz, $-SCH_2CH_3$), 3.18 (t, 4H, J = 7 Hz, 2 x $-C\underline{H}_2I$) and 4.20 (q, 2H, J = 7 Hz, $-OC\underline{H}_2CH_3$); ms M^+ 567.9974 (calcd. for $C_{17}H_{30}O_3SI_2$: 568.0009). Adduct 63 (256 mg, 20%): ir 1736 (ester carbonyl) and 1640 cm^{-1} (thiol ester carbonyl); nmr δ 1.20 (t, 6H, J = 7 Hz, 2 x $-SCH_2C\underline{H}_3$), 1.22 (t, 6H, J = 7 Hz, 2 x $-OCH_2C\underline{H}_3$), 2.85 (q, 4H, J = 7.5 Hz, 2 x $-SC\underline{H}_2CH_3$), 3.57 (t, 2H, J = 7 Hz, 2 x -COCHCO-) and 4.22 (q, 4H, J = 7.5 Hz, $-OC\underline{H}_2CH_3$), ms M^+ 420.1643 (calcd. for $C_{19}H_{32}O_6S_2$: 420.1640).

Reaction of iodo adduct 61 with sodium hydride

A solution of iodo compound 61 (381 mg, 1.02 mmol) in tetrahydrofuran (10 mL) was added to a suspension of sodium hydride (61.5 mg, 2.05 mmol) in tetrahydrofuran (5 mL). The solution was stirred at room temperature under an argon atmosphere for 24 h. The reaction mixture was quenched with ice-cold 1 N hydrochloric acid solution then extracted with dichloromethane (3 x 20 mL). The extracts were combined, washed with saturated sodium chloride solution, dried, filtered, and concentrated. The residue was purified by flash chromatography eluting with 10% ether in petroleum ether to afford pure ester 60 (243 mg, 97% yield). The spectral results (ir, ^1H nmr and ms) were identical to those already reported (vide supra).

Addition of 1-iodopropane to thiolester 53

A solution of thiolester **53** (347 mg, 1.70 mmol) in tetrahydrofuran (2 mL) was added dropwise to a suspension of sodium hydride (77 mg, 2.57 mmol) in tetrahydrofuran (10 mL) at 0°C. The reaction mixture was stirred under an argon atmosphere at room temperature for 5 min. The solution of 1-iodopropane (0.20 mL, 2.05 mmol) in tetrahydrofuran (3 mL) was added and the mixture refluxed for 20 h. The mixture was cooled then quenched with ice-cold 1 N aqueous hydrochloric acid solution and extracted with dichloromethane. The extracts were combined, washed with saturated sodium chloride solution, dried, filtered and concentrated. Bulb-to-bulb distillation of the crude product at 48°C/1 torr afforded compound **64** (382 mg, 91% yield): ir 1740 (ester carbonyl) and 1648 cm^{-1} (thiolester carbonyl); nmr δ 0.83 (t, 3H, J = 7 Hz, $-CH_3$), 0.95 (t, 3H, J = 7 Hz, $-CH_3$), 1.22 (t, 3H, J = 7 Hz, $-SCH_2C\underline{H_3}$), 1.25 (t, 3H, J = 7 Hz, $-OCH_2C\underline{H_3}$), 1.92 (t, 2H, J = 8 Hz, $-C\underline{H_2}-$), 2.00 (q, 2H, J = 7 Hz, $-C\underline{H_2}CH_3$), 2.90 (q, 2H, J = 7 Hz, $-SC\underline{H_2}CH_3$) and 4.20 (q, 2H, J = 7 Hz, $-OC\underline{H_2}CH_3$); ms M^+ 246.1293 (calcd. for $C_{12}H_{22}O_3S$: 246.1290).

Addition of 2-iodopropane to adduct 53

A solution of thiolester 53 (402 mg, 1.97 mmol) in tetrahydrofuran (3 mL) was added dropwise to a suspension of sodium hydride (89 mg, 2.97 mmol) in tetrahydrofuran (10 mL) at 0°C. The reaction mixture was stirred under an argon atmosphere at room temperature for 5 min. A solution of 2-iodopropane (0.24 mL, 2.40 mmol) in tetrahydrofuran (3 mL) was added and the mixture refluxed for 20 h. The mixture was cooled then quenched with ice-cold 1 N aqueous hydrochloric acid solution and extracted with dichloromethane. The extracts were combined, washed with saturated sodium chloride solution, dried, filtered and concentrated. Bulb-to-bulb distillation of the crude product at 45°C/1 torr afforded compound 65 (426 mg, 87% yield): ir 1740 (ester carbonyl) and 1646 cm^{-1} (thiolester carbonyl); nmr δ 0.86 (t, 3H, J = 7 Hz, $-CH_2C\underline{H}_3$), 0.94 (d, 3H, J = 7 Hz, $C\underline{H}_3\overset{|}{C}HCH_3$), 1.02 (d, 3H, J = 7 Hz, $CH_3\overset{|}{C}HC\underline{H}_3$), 1.25 (t, 3H, J = 7 Hz, $-SCH_2C\underline{H}_3$), 1.28 (t, 3H, J = 7 Hz, $-OCH_2C\underline{H}_3$), 1.98 (m, 1H, J = 7 Hz, $-\overset{|}{C}H-$), 2.07 (m, 1H, J = 7 Hz, $-CH\underline{H}CH_3$), 2.36 (m, 1H, J = 7 Hz, $-C\underline{H}HCH_3$), 2.92 (q, 2H, J = 7 Hz, $-SC\underline{H}_2CH_3$) and 4.20 (q, 2H, J = 7 Hz, $-OC\underline{H}_2CH_3$); ms M^+ 246.1298 (calcd. for $C_{12}H_{22}O_3S$: 246.1290).

Raney nickel reduction of adduct **47**

A solution of ester **47** (387 mg, 2.04 mmol) in benzene (5 mL) was added to a suspension of Raney nickel (5 mL, settled volume) in benzene (10 mL). The mixture was stirred under an argon atmosphere at room temperature for 4 h and then filtered. The residue was washed thoroughly with benzene and then absolute ethanol (3 x 4 mL). The filtrate was then concentrated. Chromatography of crude material on silica gel, eluting with 20% ether in petroleum ether afforded the hydroxy ester **69** (225 mg, 95% yield): ir 1733 (ester carbonyl) and 3440 cm^{-1} (alcohol); nmr δ 1.15 (d, 3H, J = 8 Hz, $-CH_3$), 1.26 (t, 3H, J = 8 Hz, $-CH_2\underline{CH_3}$), 2.67 (m, 1H, $-CO\overset{|}{C}\underline{H}CH_2OH$), 3.70 (m, 2H, $-C\underline{H_2}OH$), and 4.15 (q, 2H, J = 8 Hz, $-OC\underline{H_2}CH_3$); ms m/z 102.0686 (M^+ -30; calcd. for $C_5H_{10}O_2$: 102.0681). Anal. Calcd. for $C_6H_{12}O_3$: C 54.79, H 9.87; Found: C 54.79, H 9.83.

Reduction of compound **49** with Raney nickel

To a solution of ester **49** (1.827 g, 6.87 mmol) in benzene (20 mL) was added freshly prepared Raney nickel (10 mL, settled volume) in benzene (10 mL). The mixture was stirred under argon atmosphere at room temperature for 4 h and then filtered. The residue was thoroughly washed with benzene and then ethanol (3 x 4 mL). The filtrate was then concentrated. Flash chromatography of the residue on silica gel, eluting with 20% ether in petroleum ether followed by bulb-to-bulb distillation at 60°C/1 torr afforded the hydroxy ester **66** (1.327 g, 93% yield): ir 3445 (hydroxyl), 1732 (ester), 1580 and 1600 cm^{-1} (phenyl); nmr δ 1.22 (t, 3H, J = 7 Hz, $-OCH_2C\underline{H}_3$), 2.22 (br, s, 1H, -OH) 2.63 (m, 1H, $-CO\overset{|}{C}\underline{H}CH_2OH$), 2.93 (br, d, 2H, J = 7.5 Hz, $-C\underline{H}_2Ph$), 3.72 (br, d, J = 7.5 Hz, 2H, $-C\underline{H}_2OH$) and 4.15 (q, 2H, J = 7 Hz, $-OC\underline{H}_2CH_3$); ms M^+ 208.1100 (calcd. for $C_{12}H_{16}O_3$: 208.1099). Anal. Calcd. for $C_{12}H_{16}O_3$: C 69.21, H 7.69; Found: C 69.23, H 7.52.

Reduction of adduct **48** with Raney nickel

A solution of compound **48** (424 mg, 2.08 mmol) in benzene (5 mL) was added to a suspension of Raney nickel (5 mL, settled volume) in benzene (10 mL). The mixture was stirred under an argon atmosphere at room temperature for 4 h and then filtered. The residue was thoroughly washed with benzene and then absolute ethanol (2 x 5 mL). The filtrate was then concentrated. Chromatography of the crude material on silica gel, eluting with 20% ether in petroleum ether afforded the hydroxy ester **70** (294 mg, 97% yield): ir 3440 (alcohol) and 1736 (esters); nmr δ 1.15 (s, 6H, $-\overset{|}{C}(C\underline{H}_3)_2$), 1.26 (t, 3H, J = 7.5 Hz, $-OCH_2C\underline{H}_3$), 2.22 (br, s, $-O\underline{H}$), 3.60 (br, s, $-C\underline{H}_2OH$) and

4.16 (q, 2H, J = 7.5 Hz, $-OC\underline{H}_2CH_3$); ms m/z 116.0836 (M^+ -30, calcd. for $C_6H_{12}O_2$: 116.0837).

Reduction of ester **51**

A solution of adduct **51** (1.562 g, 5.87 mmol) in benzene (5 mL) was added to a suspension of Raney nickel (8 mL, settled volume) in benzene (20 mL). The mixture was stirred under an argon atmosphere at room temperature for 4 h and then filtered. The residue was thoroughly washed with benzene (3 mL) and ethanol (4 x 5 mL). The filtrate was concentrated. Bulb-to-bulb distillation at 68°C/1 torr afforded hydroxy ester **71** (1.04 g, 85% yield): ir 3440 (hydroxyl) and 1736 cm^{-1} (ester carbonyl); nmr δ 1.28 (t, 3H, J = 7 Hz, $-OCH_2C\underline{H}_3$), 1.64 (br, s, 1H, -OH), 1.96 (q, 2H, J = 7 Hz, $-\overset{|}{C}HC\underline{H}_2CH_2-$), 2.38 (t, 2H, J = 7 Hz, $-CH_2CO-$), 2.62 (m, 1H, $-CO\overset{|}{C}\underline{H}CH_2OH$), 3.68 (s, 3H, $-OCH_3$), 3.78 (br, t, 2H, J = 6 Hz, $-C\underline{H}_2OH$) and 4.20 (q, 2H, J = 7 Hz, $-OC\underline{H}_2CH_3$); ms m/z 173.0811 (M^+-31, calcd. for $C_8H_{13}O_4$: 173.0814). *Anal*. Calcd. for $C_9H_{16}O_6$: C 52.94, H 7.84; Found: C 53.02, H 7.89.

Reduction of adduct **53**

A solution of adduct **53** (541 mg, 2.65 mmol) in benzene (10 mL) was added to a suspension of Raney nickel (7 mL, settled volume) in benzene. The mixture was stirred under an argon atmosphere for 4 h and then filtered. The residue was washed thoroughly with benzene (3 mL) and ethanol (3 x 4 mL). The filtrate was then concentrated. Chromatography of the crude material on silica gel, eluting with 20% ether in petroleum ether afforded the hydroxy ester **72** (306 mg, 79% yield): ir 1729 (ester carbonyl) and 3441 cm^{-1} (alcohol); nmr δ 0.97 (t, 3H, J = 8 Hz, $-CH_2C\underline{H_3}$), 1.28 (t, 3H, J = 8 Hz, $-OCH_2C\underline{H_3}$), 1.63 (m, 2H, $-C\underline{H_2}CH_3$), 2.10 (br, s, 1H, -OH), 2.52 (m, 1H, $-\overset{|}{C}H-$), 3.75 (br, d, 2H, $-CH_2OH$) and 4.20 (q, 2H, J = 8 Hz, $-OC\underline{H_2}CH_3$); ms m/z 116.0839 (M^+-31, calcd. for $C_6H_{12}O_2$: 116.0834). Anal. Calcd. for $C_7H_{14}O_3$: C 57.51, H 9.65; Found: C 57.43, H 9.72.

Reduction of adduct 54

A solution of adduct **54** (347 mg, 1.59 mmol) in benzene (5 mL) was added to a suspension of Raney nickel (5 mL, settled volume) in benzene. The mixture was stirred under an argon atmosphere at room temperature for 4 h and then filtered. The residue was washed thoroughly with benzene and then ethanol (2 x 5 mL). The filtrate was then concentrated. Flash chromatography of the crude material on silica gel eluting with 20% ether in petroleum ether afforded the hydroxy ester **73** (219 mg, 86%): ir 3440 (alcohol) and 1733 cm^{-1} (ester carbonyl); nmr δ 0.92 (t, 3H, J = 7 Hz, $-(CH_2)_2C\underline{H_3}$), 1.30 (t, 3H, J = 7 Hz,

$-OCH_2C\underline{H_3}$), 1.56 (m, 4H, $-(C\underline{H_2})_2CH_3$), 2.22 (br, s, 1H, $-OH$), 2.58 (m, 1H, $-CO\overset{|}{C}\underline{H}CH_2OH$), 3.75 (br, d, 2H, $-C\underline{H_2}OH$) and 4.20 (q, 2H, J = 7 Hz, $-OC\underline{H_2}CH_3$); ms M^+ 160.1098 (calcd. for $C_8H_{16}O_3$: 160.1099). Anal. Calcd. for $C_8H_{16}O_3$: C 59.98, H 10.07; Found: C 59.92, H 10.11.

Reduction of thiolester 55

A solution of thiolester **55** (224 mg, 1.27 mmol) in benzene (5 mL) was added to a suspension of Raney nickel (4 mL, settled volume) in benzene (10 mL). The mixture was stirred under an argon atmosphere at room temperature for 4 h and then filtered. The residue was washed thoroughly with benzene and then ethanol (2 x 3 mL). The filtrate was then concentrated. Flash chromatography of the crude product on silica gel eluting with 20% ether in petroleum ether afforded the hydroxy ester **74** (153 mg, 98% yield): ir 3440 (alcohol) and 1732 cm^{-1} (ester carbonyl); nmr δ 0.96 (d, 3H, J = 7 Hz, $-CH(C\underline{H_3})CH_3$), 0.98 (d, 3H, J = 7 Hz, $-CH(CH_3)C\underline{H_3}$), 1.20 (t, 3H, J = 7 Hz, $-OCH_2C\underline{H_3}$), 2.38 (m, 1H, $-C\underline{H}(CH_3)_2$), 3.50 (q, 1H, J = 7 Hz, $-CO\overset{|}{C}\underline{H}CH_2OH$), 3.75 (d, 2H, J = 7 Hz, $-C\underline{H_2}OH$) and 4.21 (q, 2H, J = 7 Hz, $-OC\underline{H_2}CH_3$); ms M^+ 160.1098 (calcd. for $C_8H_{16}O_3$: 160.1099).

Reduction of ester 56 with Raney nickel

To a slurry of Raney nickel (7 mL, settled volume) in benzene (15 mL) was added a solution of adduct **56** (1.07 g, 3.72 mmol) in benzene (10 mL). The mixture was stirred under an argon atmosphere at room temperature for 6 h and then carefully filtered. The residue was thoroughly washed with benzene and then ethanol (2 x 4 mL). The filtrate was then concentrated. Flash chromatography of the residue on silica gel, eluting with 20% ether in petroleum ether afforded the hydroxy ester **75** (847 mg, 98%): ir 3450 (alcohol) and 1736 cm^{-1} (ester carbonyl); nmr δ 0.86 (t, 3H, J = 7 Hz, $-(CH_2)_7C\underline{H_3}$), 1.28 (m, 15H, $-OCH_2C\underline{H_3}$, $-CH_2(C\underline{H_2})_6CH_3$), 1.62 (m, 2H, $-\overset{|}{C}HC\underline{H_2}(CH_2)_6CH_3$), 2.56 (m, 1H, J = 7 Hz, $-CO\overset{|}{C}\underline{H}CH_2OH$), 3.73 (br, d, J = 7 Hz, $-CH_2OH$) and 4.18 (q, 2H, J = 7 Hz, $-OC\underline{H_2}CH_3$); ms M^+ 230.1881 (calcd. for $C_{13}H_{26}O_3$: 230.1882). *Anal*. Calcd. for $C_{13}H_{26}O_3$: C 60.00, H 10.07; Found: C 60.31, H 10.33.

Reduction of adduct 57 to hydroxy ester 76

A solution of adduct **57** (423 mg, 1.82 mmol) in benzene (5 mL) was added to a suspension of Raney nickel (6 mL, settled volume) in benzene. The mixture was stirred under an argon atmosphere at room temperature for 3 h and then filtered. The residue was washed thoroughly with benzene and then absolute ethanol (2 x 5 mL). The filtrate was then concentrated. Chromatography of crude material on silica gel, eluting with 20% ether in petroleum ether afforded the hydroxy ester **76** (310 mg, 98%): ir 3440 (hydroxy) and 1728 cm^{-1} (ester carbonyl); nmr δ 0.89 (t, 6H, J = 7.5 Hz, 2 x $-CH_2C\underline{H_3}$), 1.29 (t, 3H, J = 7.5 Hz, $-OCH_2C\underline{H_3}$), 1.62 (q, 4H, J = 7.5 Hz, 2 x $-C\underline{H_2}CH_3$), 3.68 (s, 2H, $-C\underline{H_2}OH$) and 4.18 (q, 2H, J = 7.5 Hz, $-OC\underline{H_2}CH_3$); ms m/z 144.1149 (M^+-30, calcd. for $C_8H_{16}O_2$: 144.1150). Anal. Calcd. for $C_9H_{18}O_3$: C 66.63, H 11.18; Found: C 66.52, H 11.13.

Reduction of thiolester 58 with Raney nickel

A solution of thiolester **58** (277 mg, 1.03 mmol) in benzene (5 mL) was added to a suspension of freshly prepared Raney nickel (4 mL, settled volume) in benzene (10 mL). The mixture was stirred under an argon atmosphere at room temperature for 6 h and then filtered. The residue was thoroughly washed with benzene and ethanol (2 x 5 mL). The filtrate was then concentrated. Flash chromatography of the crude product on silica gel, eluting with 20% ether in petroleum ether afforded the hydroxy ester **77** (211 mg, 95% yield): ir 1728 cm^{-1} (ester carbonyl) and 3440 cm^{-1} (alcohol); nmr δ 0.88 (t, 6H, J = 7 Hz, 2 x $-(CH_2)_2C\underline{H_3}$), 2.20 (br, s, 1H, -OH), 3.68 (br, d, 2H, J = 3.5 Hz, $-C\underline{H_2}OH$) and 4.15 (t, 2H, J = 7 Hz,

$-OC\underline{H_2}CH_3$); ms M^+ 202.1566 (calcd. for $C_{11}H_{22}O_3$: 202.1569).

Reduction of thiolester 59 with Raney nickel

A solution of thiolester **59** (682 mg, 2.37 mmol) in benzene (6 mL) was added to a suspension of freshly prepared Raney nickel (7 mL, settled volume) in benzene (15 mL). The reaction mixture was stirred under an argon atmosphere at room temperature for 6 h and then filtered. The residue was thoroughly washed with benzene (4 mL) and ethanol (3 x 5 mL). The filtrate was concentrated. Flash chromatography of the crude product on silica gel, eluting with 20% ether in petroleum ether afforded the hydroxy ester **78** (496 mg, 91% yield): ir 3440 (hydroxy) and 1728 cm^{-1} (ester carbonyl); nmr 0.86 (t, 6H, J = 7 Hz, 2 x $-(CH_2)_3C\underline{H_3}$), 2.22 (br, s, 1$\underline{H}$, -OH), 3.67 (br, d, 2H, J = 3.5 Hz, $-C\underline{H_2}OH$) and 4.20 (t, 2H, J = 7 Hz, $-OC\underline{H_2}CH_3$); ms M^+ 230.1881 (calcd. for $C_{13}H_{26}O_3$: 230.1882).

Raney nickel reduction of thiolester 60

A solution of adduct **60** (1.869 g, 4.10 mmol) in benzene (10 mL) was added to a suspension of freshly prepared Raney nickel (10 mL, settled volume) in benzene (20 mL). The reaction mixture was stirred under an argon atmosphere at room temperature for 6 h and then filtered carefully. The residue was thoroughly washed with benzene (2 x 3 mL) and ethanol (4 x 5 mL). The filtrate was then concentrated. Flash chromatography of the residue on silica gel, eluting with 20% ether in petroleum ether afforded pure hydroxy ester **79** (1.306 g, 96% yield): ir 1725, 1732 (ester carbonyl), 3456 and 3466 cm^{-1} (alcohol); nmr 1.26 (t, 3H, J = 7 Hz, $-CH_2\underline{CH_3}$), 1.42 (m, 10H, cyclohexyl protons), 2.16 (br, s, 1H, $-O\underline{H}$), 3.62 (s, 2H, $-\underline{CH_2}OH$) and 4.18 (q, 2H, J = 7 Hz, $-O\underline{CH_2}CH_3$); ms M^+ 186.1255 (calcd. for $C_{10}H_{18}O_3$: 186.1256). Anal. Calcd. for $C_{10}H_{18}O_3$: C 64.49, H 9.74; Found: C 64.44, H 9.63.

Dehydration of hydroxy ester **71** via mesylate

To a solution of hydroxy ester **71** (846 mg, 4.15 mmol) in freshly distilled dichloromethane (20 mL) was added methanesulfonyl chloride (0.963 mL, 12.44 mmol) and the mixture was stirred for 10 min at 0°C under an argon atmosphere. Triethylamine (2.89 mL, 20.73 mmol) was added slowly *via* a syringe and the mixture continued stirring for 6 h at room temperature. The reaction mixture was concentrated under reduced pressure and resulting yellow solids were redissolved in benzene (25 mL). 1,8-Diazabicyclo[5.4.0]undec-7-ene (1.55 mL) was added and the mixture heated at reflux under an argon atmosphere for 5 h. The mixture was then cooled at room temperature, acidified with 1 N hydrochloric acid solution and extracted with dichloromethane (4 x 25 mL). The extracts were combined and washed successfully with aqueous saturated sodium carbonate solution and saturated sodium chloride solution. The combined extract was dried, filtered, and concentrated. The crude product was purified by flash chromatography on silica gel (10% ether in petroleum ether as eluent) to give olefin **80** (585 mg, 76% yield): ir 1740 and 1718 (ester carbonyls), 1635 cm^{-1} (C=C); nmr δ 1.25 (t, 3H, J = 7 Hz, $-OCH_2C\underline{H_3}$), 2.28 (br, t, 2H, J = 7 Hz, $-CH_2\overset{|}{C}=$), 2.38 (t, 2H, J = 7 Hz, $-CH_2C\underline{H_2}CO-$), 3.68 (s, 3H, $-OCH_3$), 4.20 (q, 2H, J = 7 Hz, $-OC\underline{H_2}CH_3$), 5.60 (d, 1H, J = 1 Hz, $=C\underline{H}H$) and 6.20 (br, s, 1H, $=CH\underline{H}$); ms M$^+$ 186.0892 (calcd. for $C_9H_{14}O_4$: 186.0892). Anal. Calcd. for $C_9H_{14}O_4$: C 58.06, H 7.53; Found: C 57.93, H 7.59.

Dehydration of hydroxy ester **66** via mesylate

To a solution of hydroxy ester **66** (1.027 g, 4.94 mmol) in freshly distilled dichloromethane (20 mL) was added methanesulfonyl chloride (1.15 mL, 14.86 mmol) and the mixture stirred for 10 min at 0°C under an argon atmosphere. Triethylamine (3.44 mL, 24.68 mmol) was added slowly *via* a syringe and the mixture was stirred for 6 h at room temperature. The reaction mixture was then concentrated under reduced pressure and the resulting yellow solid was redissolved in benzene (25 mL). 1,8-Diazabicyclo[5.4.0]undec-7-ene (2.95 mL) was added and the mixture heated at reflux under an argon atmosphere for 5 h. The mixture was then cooled to room temperature, poured into 1 N hydrochloric acid solution and extracted with dichloromethane (3 x 25 mL). The extracts were combined and washed successfully with aqueous saturated sodium carbonate solution and saturated sodium chloride solution. The combined extract was dried, filtered, and concentrated. The residue was purified by flash chromatography on silica gel (10% ether in petroleum ether) to give olefin **82** (901 mg, 96% yield): ir 3040-3100 (aromatic), 1718 (ester carbonyl), 1636 (C=C), 1605, 1586 (phenyl), 745 and 701 cm^{-1} (monosubstituted benzene); nmr δ 1.26 (t, 3H, J = 7 Hz, $-OCH_2\underline{CH_3}$), 3.64 (br, s, 2H, $-CH_2Ph$), 4.18 (q, 2H, J = 7 Hz, $-O\underline{CH_2}CH_3$), 5.45 (d, 1H, J = 1 Hz, $=\underline{C}\underline{H}H$), 6.22 (d, 1H, J = 1 Hz, $=CH\underline{H}$) and 7.27 (m, 5H, aromatic protons); ms M$^+$ 190.0994 (calcd. for $C_{12}H_{14}O_2$: 190.0994).

Direct dehydration of hydroxy ester **75** by using dicyclohexylcarbodiimide

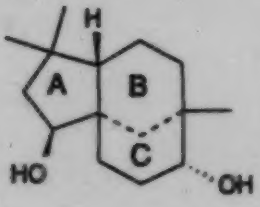
A solution of hydroxy ester **76** (713 mg, 3.10 mmol), dicyclohexylcarbodiimide (1.28 g, 6.20 mmol) and a catalytic amount of copper(I) chloride (5 mg) in dry ether (20 mL) was heated at reflux for 12 h under an argon atmosphere. The mixture was then cooled to room temperature, diluted with ether and filtered. Concentration of the filtrate, followed by purification of the crude product by flash chromatography on silica gel using 20% ether in petroleum ether as an eluent gave olefin 83 (609 mg, 92% yield) as a colourless oil: ir 1719 (ester carbonyl) and 1625 cm^{-1} (C=C stretching); nmr δ 0.86 (t, 3H, J = 7 Hz, $-C\underline{H_3}$), 1.26 (t, 3H, J = 7 Hz, $-OCH_2C\underline{H_3}$), 2.25 (br, t, 2H, J = 7 Hz, $-CH_2-\overset{|}{C}=$), 4.20 (q, 2H, J = 7 Hz, $-OC\underline{H_2}CH_3$), 5.50 (dd, 1H, J = J' = 1.5 Hz, $=C\underline{H}H$), 6.12 (d, 1H, J = 1.5 Hz, $=CH\underline{H}$); ms M^+ 212.1778 (calcd. for $C_{13}H_{24}O_2$: 212.1776).

PART II.

SYNTHETIC STUDIES OF CLOVANE-DIOL.

INTRODUCTION

(+)-Clovane-2β,9α-diol (4,4,8-trimethyltricyclo-[6.3.1.$0^{1,5}$]dodecane-2β,9α-diol) (1) is widely distributed in nature. This compound along with (-)-caryophyllene (2) and (-)-isocaryophyllene (3) were found to be the main constituents of the oil of cloves (*Eugenia caryophyllata*).[62] These sesquiterpenes were also found to occur in African capaiba oil (*Oxystigma manii* Harns)[63] and in French lavender oil.[64] Clovane-2β,9α-diol (1) was reported to occur also in essential oils of *Mentha piperita*.[65] Dev and coworkers[66] have isolated this diol



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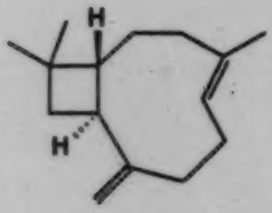

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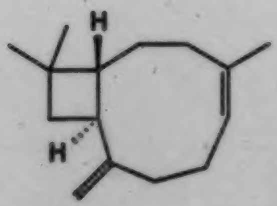


3

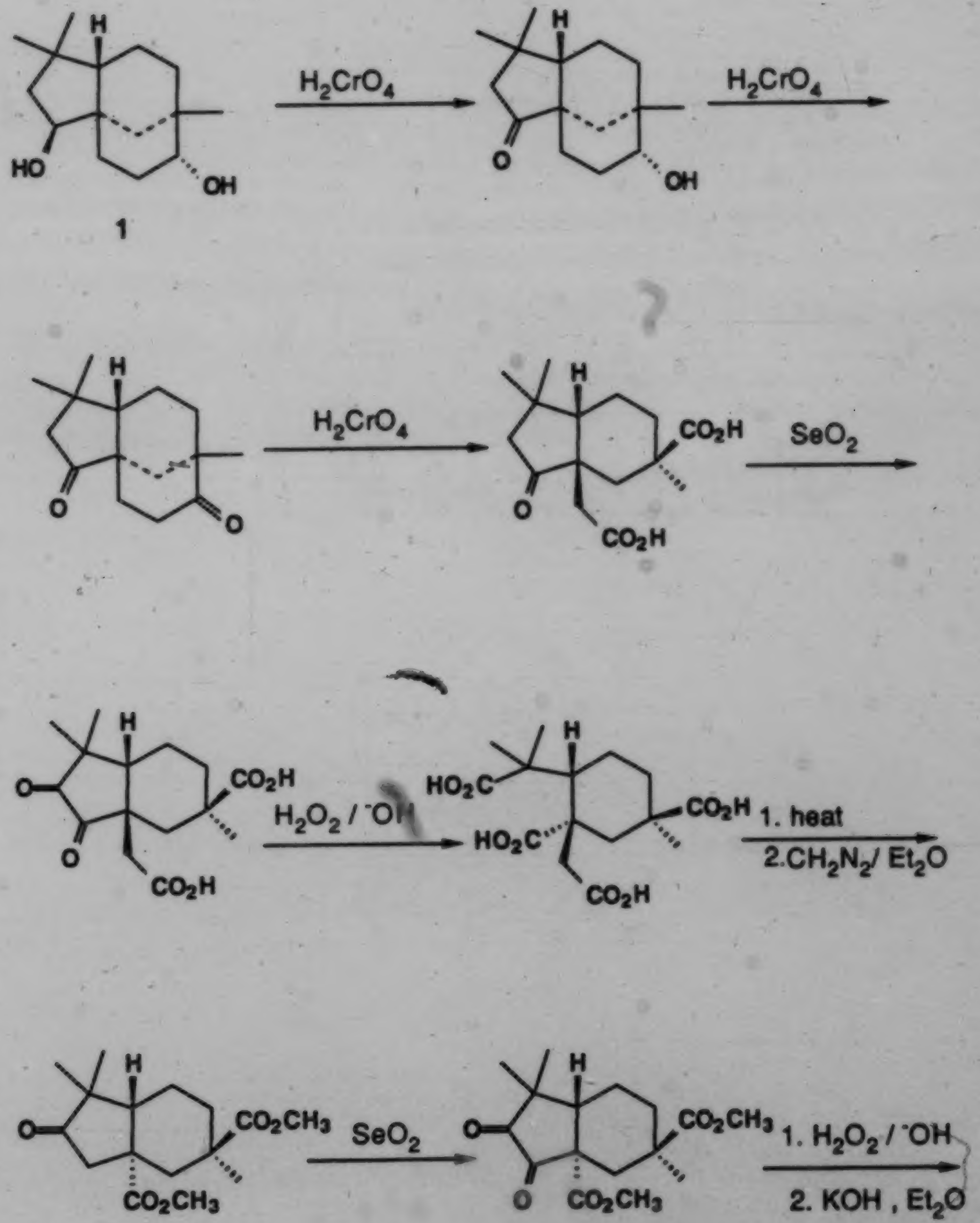
together with another complex blend of sesquiterpenes from oleoresin of *Dipterocorpus pilosus*, a tall tree occurring gregariously in Assam, India. In 1979 they also noted the presence of compound 1 in the oleoresin from *Hardwickia pinnata*,[67] a large handsome tree growing wildly in evergreen forests of Western Ghats of India. The tree, on tapping, yields in large quantities a dark or reddish brown oleoresin. Other natural sources of clovane-diol (**1**) include *Salvia canariensis*,[68] the Brazilian shrub *Bacharris megapotamica* spreng,[69] and several species of the genus *Viguiera*[70,71] such as *linearis*, *excelsa*, *oaxama*, and *hypagyrea*.

The structure of clovane-diol (**1**) was first elucidated by Barton and coworkers mainly by chemical degradation according to Scheme I.[72] The assigned structure was later confirmed by spectroscopic methods.[66,69]

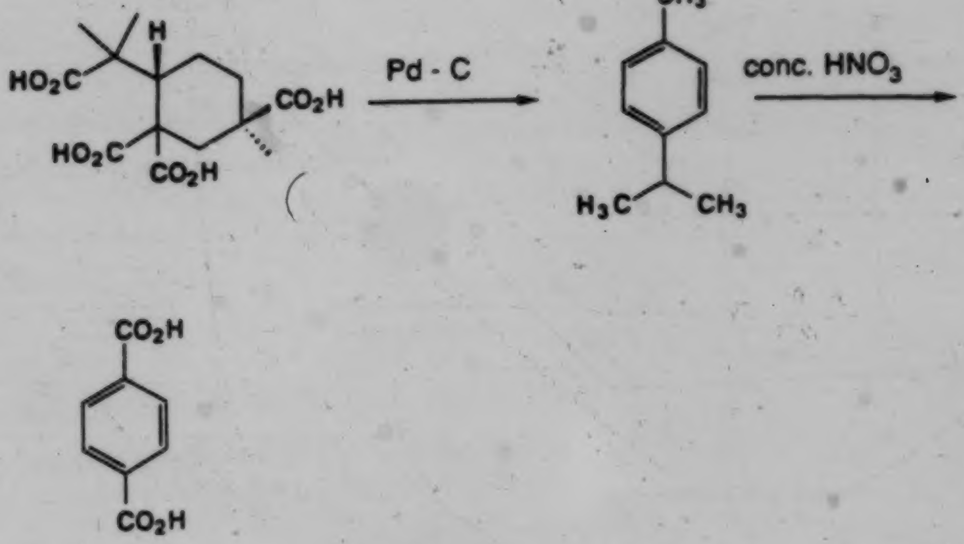
Barton and coworkers also proposed the biosynthesis of clovane-diol (**1**) as illustrated in Scheme II. This compound is believed to be produced biosynthetically from farnesyl pyrophosphate (**4**) via the intermediacy of caryophyllene (**2**) and the corresponding oxide **5**.

The conversion of caryophyllene oxide (**5**),[72,75] both from natural sources and from epoxidation of caryophyllene (**2**),[65,73] to clovane-diol (**1**) has been realized chemically.[74,76] The former compound on mild acid

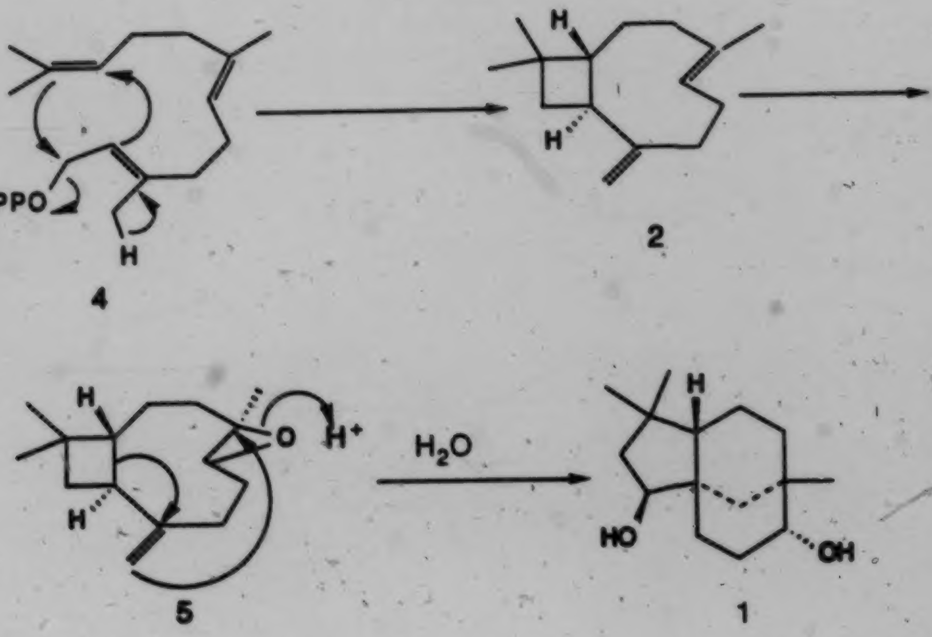
Scheme I


H
HO
OH
1
H_2CrO_4
O
H_2CrO_4
H_2CrO_4
CO_2H
SeO_2
CO_2H
H_2O_2 / ^-OH
HO_2C
HO_2C
1. heat
2. CH_2N_2/ Et_2O
CO_2CH_3
SeO_2
1. H_2O_2 / ^-OH
2. KOH , Et_2O

Scheme I (cont'd)


HO₂C
H
CO₂H
HO₂C
CO₂H
Pd - C
CH₃
H₃C
CH₃
conc. HNO₃
CO₂H
CO₂H

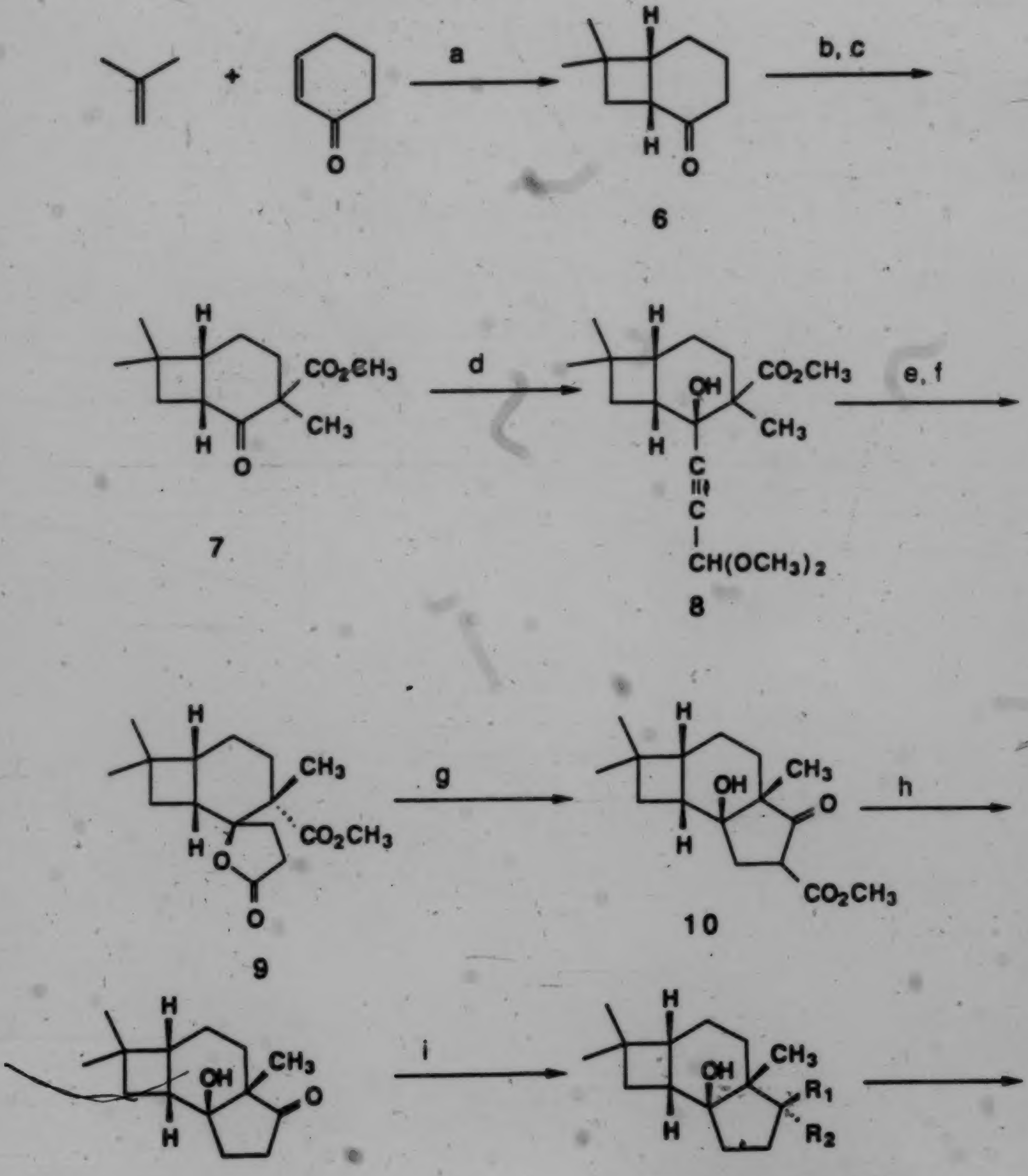
Scheme II


PPO
H
4
H
H
2
H
H
O
H⁺
5
H₂O
H
HO
OH
1

treatment resulted in the rearrangement to give **1**. Based on this finding, the configuration of compound 1 was deduced.

Although there has not been a direct attempt reported for the synthesis of clovane-diol (**1**), several formal synthesis via caryophyllene (**2**) have appeared. In the first synthesis of caryophyllene (**2**) in racemic form (Scheme III) by Corey and coworkers[77,78] in 1963, bicyclic ketone **6**, readily obtained by irradiation of a mixture of 2-cyclohexenone and isobutylene, was chosen as the key intermediate. Carbomethoxylation followed by methylation gave rise to keto ester **7**, which was then treated with the lithio salt of propargyl aldehyde dimethyl acetal to give alcohol **8**. Hydrogenation followed by oxidation in aqueous acid resulted in the formation of lactone **9**. This compound was subjected to Dieckmann condensation and the resulting keto ester **10** was hydrolyzed and decarboxylated to give ketone alcohol **11**. Raney nickel reduction of **11** gave a pair of epimeric alcohols **12** and **13** in ca. 1:1 ratio. Upon exposure to the basic conditions, the tosylate of the latter alcohol **13** underwent a 1,3-glycol type rearrangement to give the desired enone **14**, which was further epimerized to the trans-isomer **15**. Wittig reaction of **15** led to the completion of the first total synthesis of (±)-caryophyllene (**2**).

Scheme III

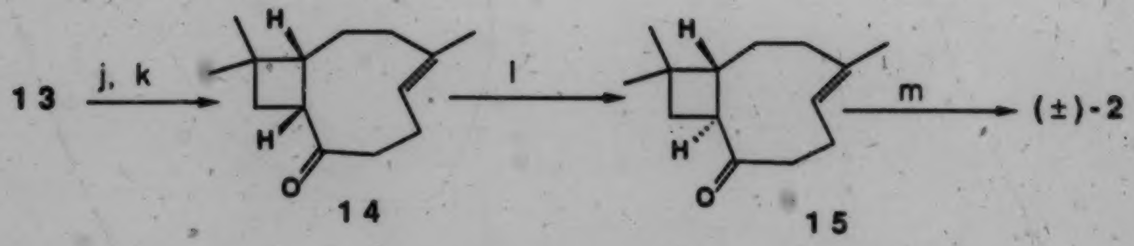

a
b, c
6
7
d
8
e, f
9
g
10
h
i
OH
CO$_2$CH$_3$
CH$_3$
CH(OCH$_3$)$_2$
R$_1$
R$_2$

11

12 R$_1$=H, R$_2$=OH

13 R$_1$=OH, R$_2$=H

Scheme III (cont'd)

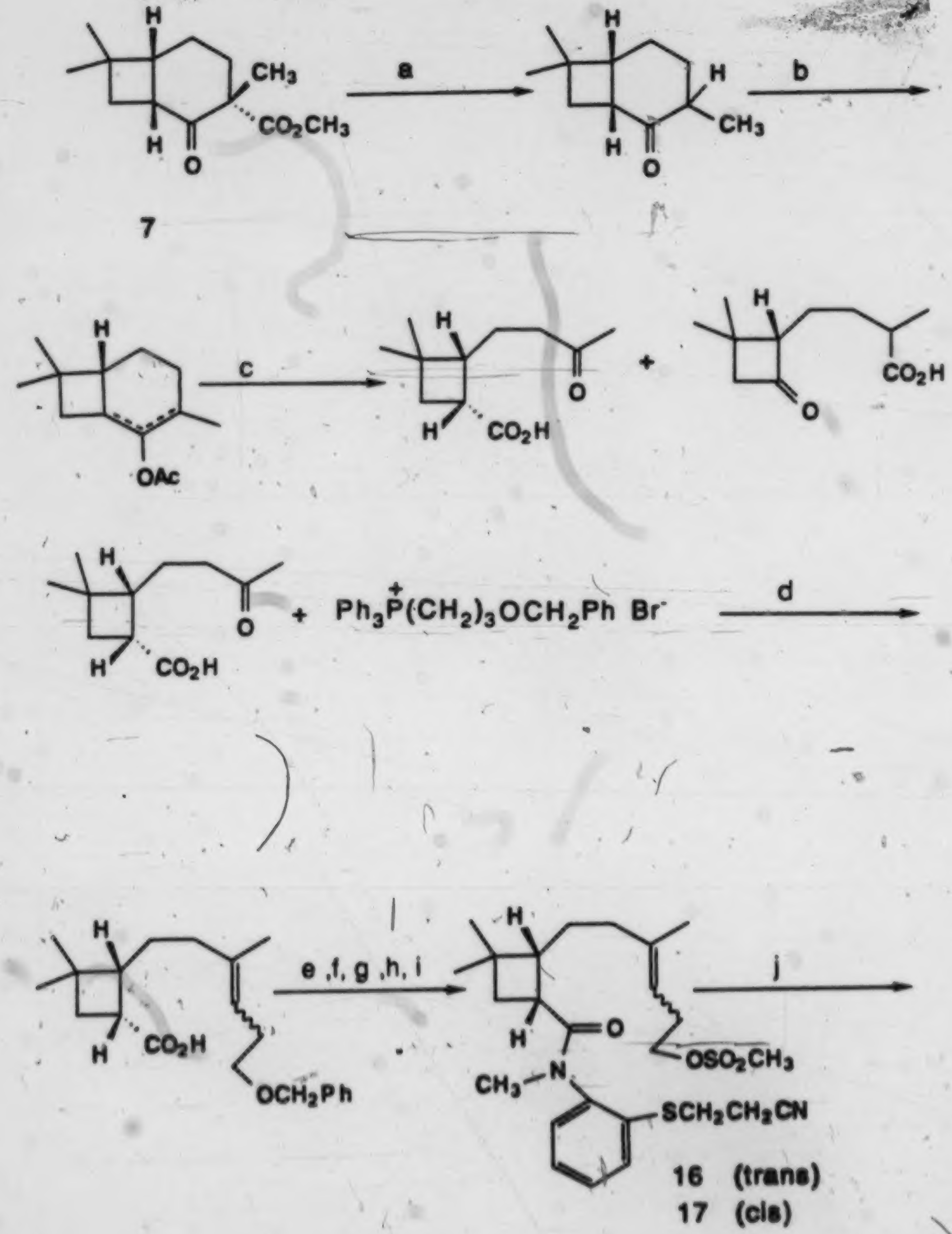


a. hv, pentane, -40°C. b. $(CH_3O)_2CO$, NaH, dioxane. c. MeI, NaH, dioxane. d. $Li^{+}\,{}^{-}CCCH(OCH_3)_2$, THF, 0°C. e. H_2, 5% Pd - C, CH_3OH. f. CrO_3, aq. CH_3CO_2H. g. $CH_3SOCH_2^{-}\,Na^{+}$, DMSO. h. aq. NaOH, 40°C; Py, 110 - 115°C. i. Ra -Ni, H_2. j. p-TsCl, Py, 22°C. k. $Na^{+}\,{}^{-}\,CH_2SOCH_3$, DMSO, 25°C. l. t-BuO^{-} Na^{+},DMSO, 25°C. m. $CH_2{=}P(Ph)_3$, DMSO, R. T.

Some twenty years later the use of compound 7 in the synthesis of caryophyllene (2) and isocaryophyllene (3) was reinvestigated by Oishi and coworkers.[79] By a sequence of reactions including decarboxylation, enol acetate formation, ozonolysis, side chain extension and modification according to Scheme IV, a mixture of two isomeric olefins 16 and 17 was obtained. The former was converted to (±)-caryophyllene (2) *via* two cyclization reactions; the first one to induce the carbon-sulfur bond formation (16 → 18) and the second one to effect the formation of the required carbocyclic system (19   20). Application of the same synthetic sequence to the *cis*-isomer 17 resulted in the synthesis of (±)-isocaryophyllene (3). These authors also devised a new strategy for the synthesis of compound 25 using cyclobutene 21 as the starting material (Scheme V). This compound was subjected to Michael addition with ethyl (phenylsulfonyl)acetate. Subsequent modification of the functionalities of the adduct 22 afforded sulfone 23 which was alkylated with chloride 24 to give compound 25, the desired synthetic precursor of caryophyllene.

In 1974, Bertland and Gras[80] made use of the photocyclization of optically active allene 26 and dimethyl ketene as the key step in the synthesis of (+)-isocaryophyllene. Compound 26 was prepared in five steps from

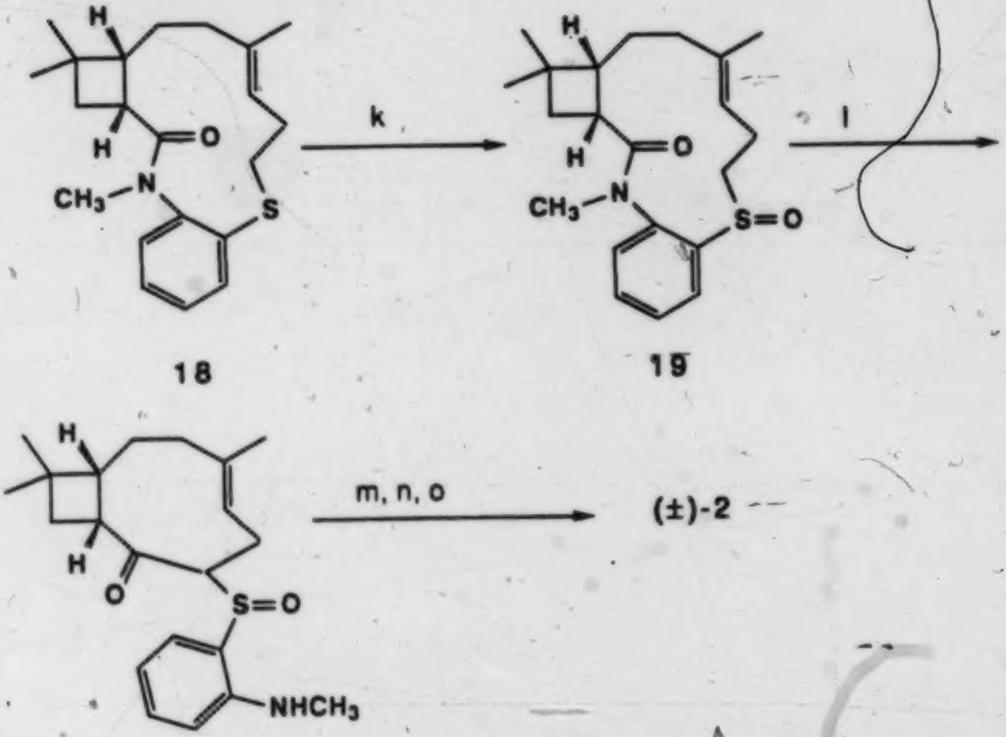
Scheme IV


H
CH3
CO2CH3
H
O
a
H
H
CH3
H
O
b
H
OAc
c
H
H
CO2H
O
+
H
CO2H
O
H
O
+
Ph3P+(CH2)3OCH2Ph Br-
d
H
CO2H
H
OCH2Ph
e ,f, g ,h, i
H
H
O
OSO2CH3
CH3
N
SCH2CH2CN
j

7

16 (trans)
17 (cis)

Scheme IV (cont'd)


H
H
O
CH_3—N
S
k
H
H
O
CH_3—N
S=O
l
H
H
O
S=O
$NHCH_3$
m, n, o
(±)-2

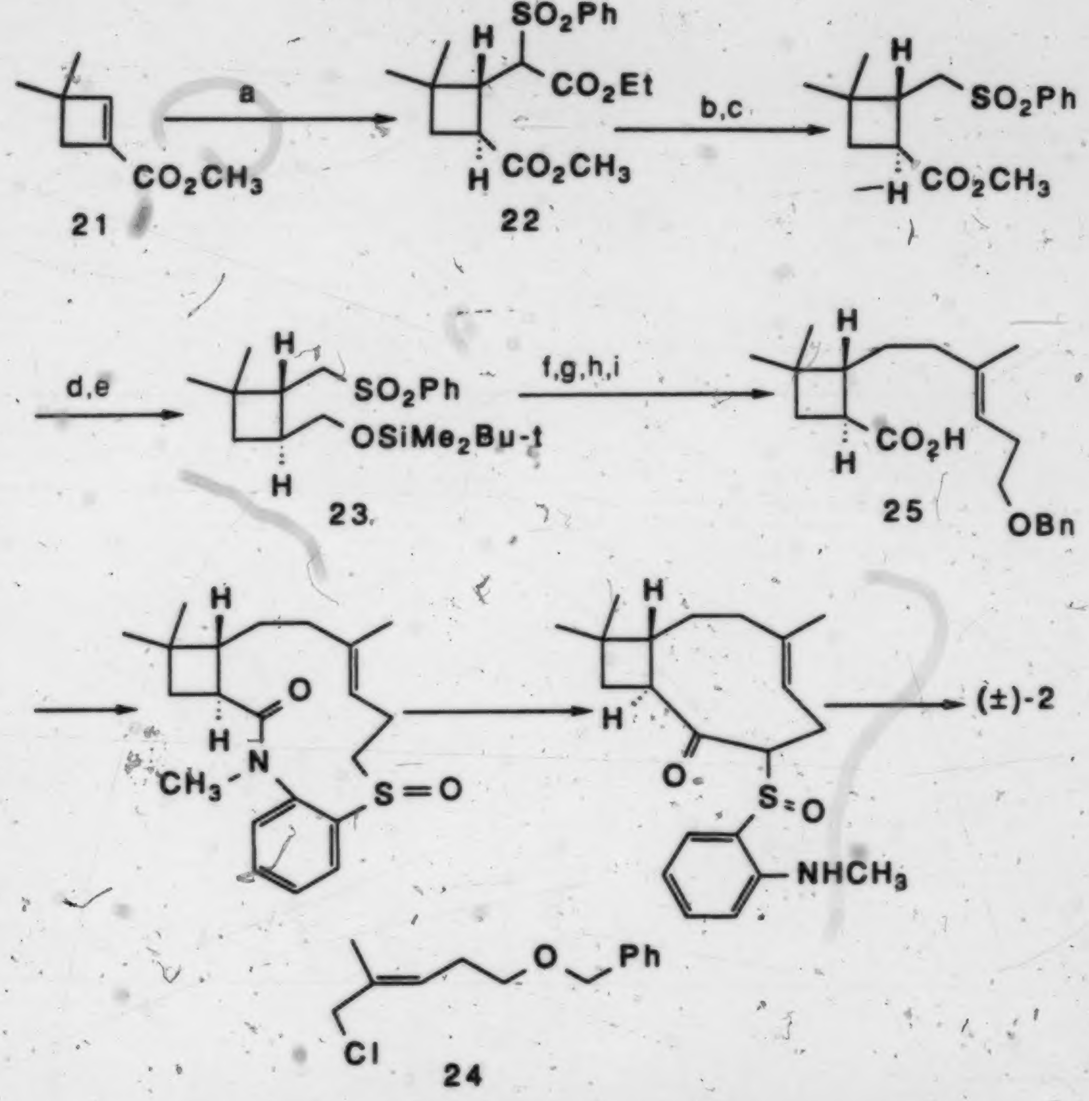
18

19

20

a. 1 N NaOH, 35 - 45°C. b. $CH_3COOCH{=}C(CH_3)_2$, PhH, reflux . c. O_3, CH_3OH, -78°C. d. BuLi, THF, 0°C to R.T. e. $(COCl)_2$, benzene, R.T. to 65°C. f. o - $Ph(NHCH_3)(SCH_2CH_2CN)$, K_2CO_3, THF, 0°C. g. $(CH_3)_2S$, BF_3 . Et_2O, Ac_2O, THF, 0°C. h. K_2CO_3, CH_3OH. i. CH_3SO_2Cl, Et_3N, CH_2Cl_2, 0°C. j. t-BuO^-K^+, t-BuOH. k. $NaIO_4$, CH_3OH, R.T. l. LDA, THF, HMPA, -78°C. m. Al - Hg, CH_3OH - H_2O. n. t-BuO^-K^+, t-BuOH. o. $CH_2{=}P(Ph)_3$, THF.

Scheme V



a
b,c
d,e
f,g,h,i
SO$_2$Ph
CO$_2$Et
CO$_2$CH$_3$
H
21
22
23
24
25
OSiMe$_2$Bu-t
CO$_2$H
OBn
O
N
CH$_3$
S=O
NHCH$_3$
Cl
Ph
(±)-2

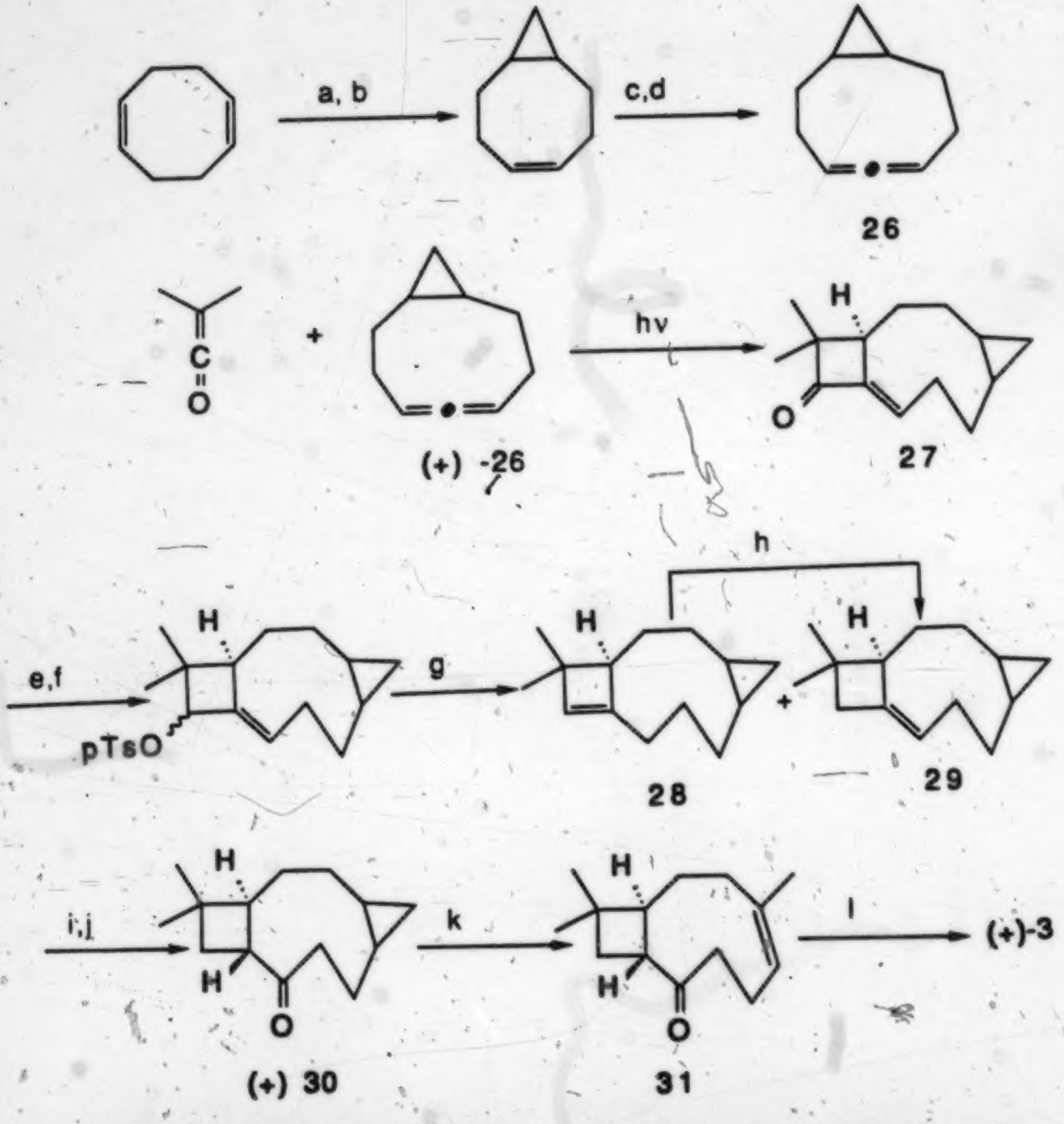
a. EtO$_2$CCH$_2$SO$_2$Ph, t-BuO$^-$ K$^+$, THF, R.T. b. 2% KOH, H$_2$O - CH$_3$CH$_2$OH, reflux ; Py, reflux . c. K$_2$CO$_3$, (CH$_3$)$_2$SO$_4$, acetone, reflux . d. LiAlH$_4$, Et$_2$O. e. t-Bu(CH$_3$)$_2$SiCl, imidazole, DMF, R.T. f. 24 , HMPA, n-BuLi, THF. g. n-Bu$_4$NF, THF. h. 5% Na - Hg, NaH$_2$PO$_4$. i. Jones reagent, 0°C.

1,5-octadiene as shown in Scheme VI. The deoxygenation of photo-adduct **27** via the corresponding alcohol gave a mixture of isomeric olefins **28** and **29** in 35:65 ratio. The former was converted to the latter by treatment with carbowax at 150°C. Hydroboration of compound **29** followed by oxidation resulted in the formation of ketone **30** which was pyrolyzed to give enone **31**. Wittig reaction of this compound afforded the enantiomer of the natural isocaryophyllene (**3**).

A very similar approach (Scheme VII) has also been used by an Indian group[81] in their synthesis of racemic isocaryophyllene (**3**). More recently, the same compound was prepared by McMurry and Miller[82] starting from ethyl geranylacetate (**32**). As shown in Scheme VIII the synthetic approach is highly efficient. Unfortunately, the trans double bond required for caryophyllene could not be retained as intended during the key coupling reaction of **33**.

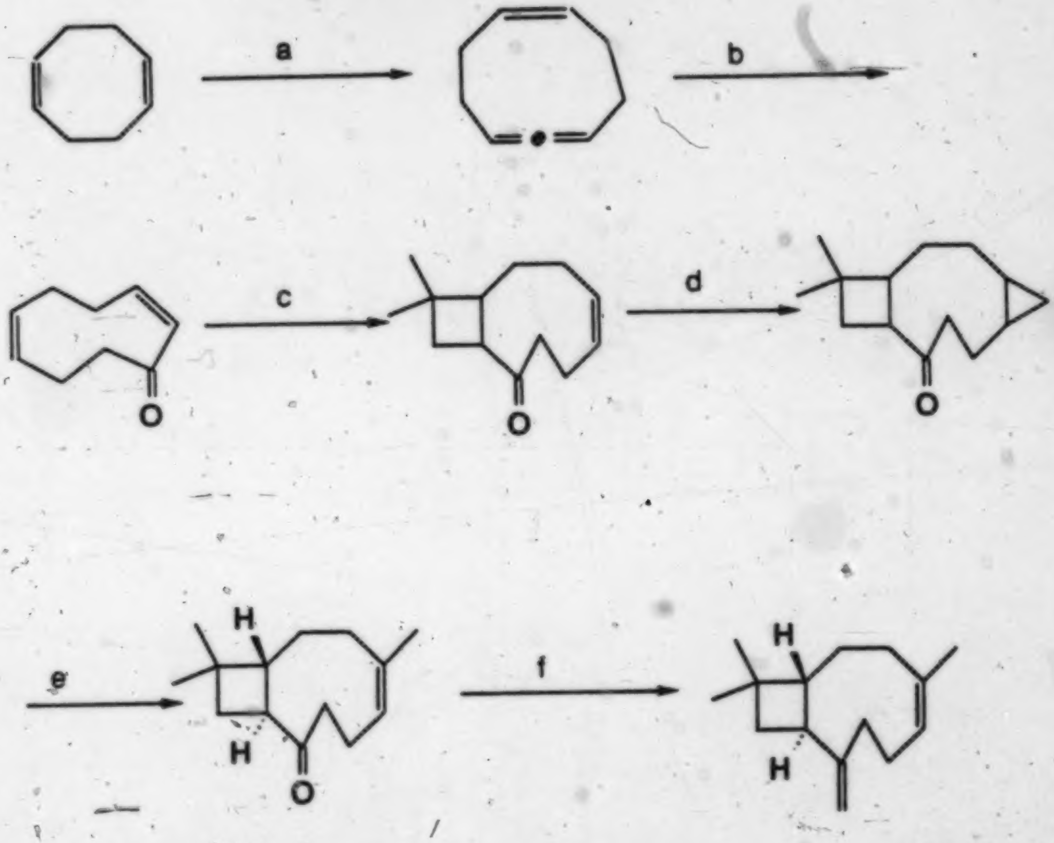
In approaches to the synthesis of (+)-clovane-diol (**1**), campholenic acid (**34**) presents itself as a highly attractive potential precursor. As can be seen in Scheme IX, this chiral substrate, which is readily accessible from the ammonium salt of (-)-10-camphorsulfonic acid (**35**) by fusion with potassium hydroxide pellets,[83] embodies nicely the complete A ring and part of B ring

Scheme VI


a, b
c,d
26
hν
(+) -26
27
h
e,f
pTsO
g
28
29
i,j
k
l
(+)-3
(+) 30
31

a. $CHCl_3$, Na^+ $^-OCH_3$. b. Li, t-BuOH. c. t-BuO$^-$ K^+, pentane, $CHBr_3$, -20°C. d. n-BuLi, -40°C. e. $LiAlH_4$. f. p-TsCl, benzene. g. $LiAlH_4$, THF, reflux . h. carbowax 20M, 150°C. i. B_2H_6 ; H_2O_2, NaOH. j. CrO_3. k. 360°C. l. $Ph_3P{=}CH_2$, DMSO.

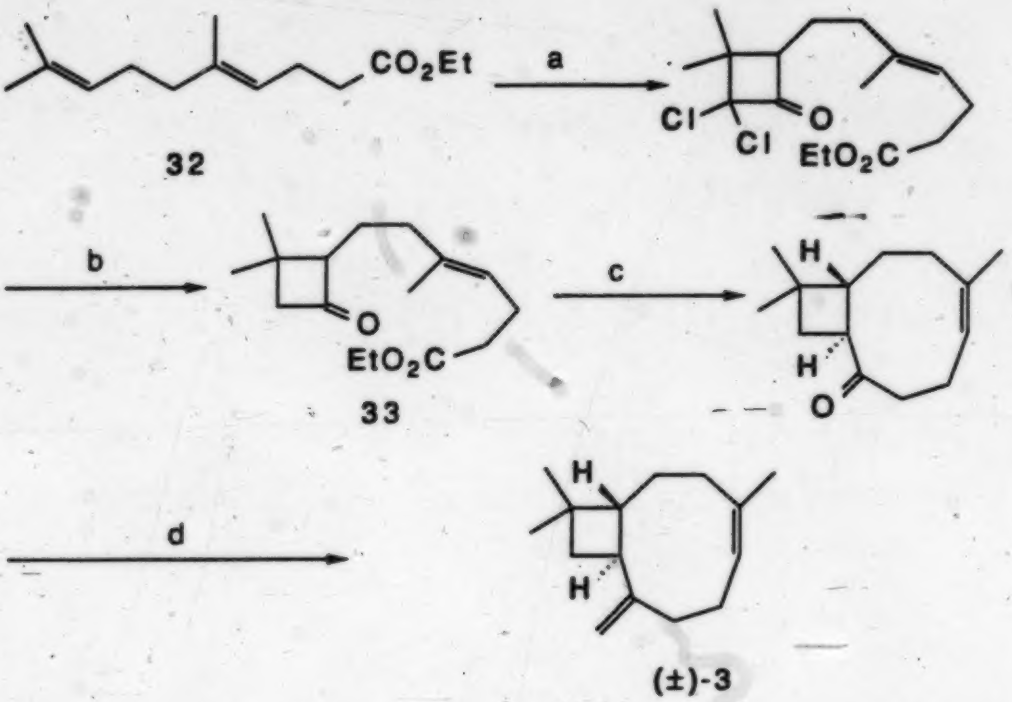
Scheme VII



(±)-3

a. CBr_4, CH_3Li, -65°C. b. B_2H_6 - THF ; CrO_3. c. $(CH_3)_2C{=}CH_2$, hv, -40 – -60°C, pentane. d. CH_2I_2, Zn - Cu. e. t-BuO⁻ K⁺, DMSO, 400°C. f. $Ph_3P{=}CH_2$, DMSO.

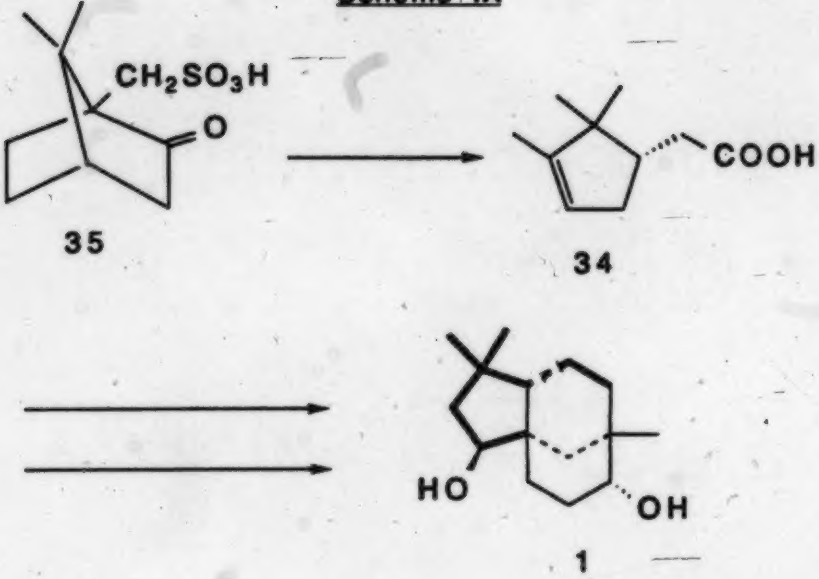
Scheme VIII



CO₂Et
32
a
Cl
Cl
O
EtO₂C
b
O
EtO₂C
33
c
H
H
O
d
H
H
(±)-3

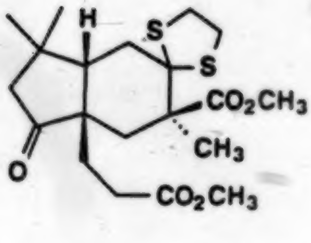
a. CCl_3COCl, $POCl_3$,Zn - Cu . b. Zn - Cu ,HOAC . c. $TiCl_3$,$LiAlH_4$, Et_3N ,then H_3O^+. d. $Ph_3P{=}CH_2$,DMSO.

Scheme IX



(bold-faced portion) of the target compound with the correct chirality. Furthermore, the functionalities of this molecule are situated adequately at the strategic positions facilitating the construction of the required framework. Based on this strategy, a project directed towards the total synthesis of natural clovane-diol (1) was initiated in our laboratory several years ago.

The second part of this thesis describes the synthesis, from camphorsulfonic acid, of compound 101, a potential precursor for clovane-diol (1).



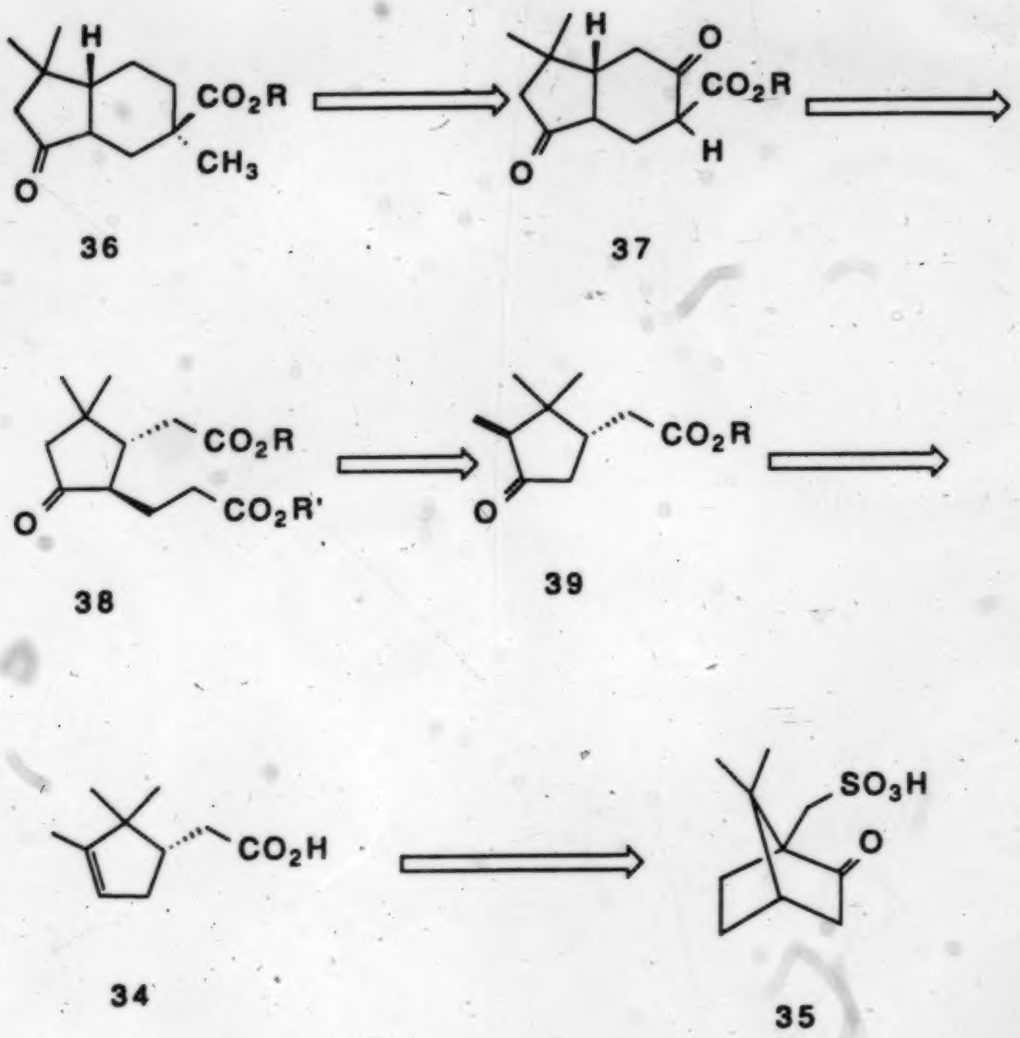
101

RESULTS AND DISCUSSION

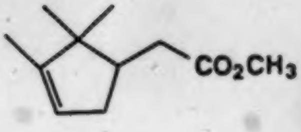
In our approach towards the synthesis of clovane-diol (**1**), a bicyclic keto ester **36** was visualized as the key intermediate. This compound represents the AB ring system of the target molecule and contains appropriate functionalities for further manipulation. From a retrosynthetic analysis (Scheme X) it was recognized that keto ester **36** could arise from diketo ester **37** by methylation and deoxygenation. The latter compound in turn could be prepared by Dieckmann condensation of diester **38**. The required propionate side chain could be installed by Michael reaction on compound **39**. This compound could arise from 10-camphorsulfonic acid (**35**) via campholenic acid (**34**) by photooxygenation (**34** → **39**).

10-Camphorsulfonic acid is readily available in levorotatory, dextrorotatory and racemic forms. For synthesis of clovane-diol (**1**) with the natural configuration, *l*-10-camphorsulfonic acid is required as starting material. At the outset of the present studies, this compound was about four times more expensive than the corresponding racemate and yet was not immediately available in our laboratory. Consequently, for preliminary exploration, the results of which are discussed below, the racemic form was used.

Scheme X

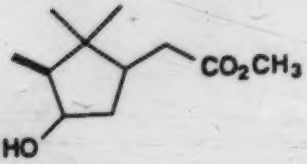

H
CO₂R
CH₃
O
36
H
O
CO₂R
H
O
37
CO₂R
CO₂R'
O
38
CO₂R
O
39
CO₂H
34
SO₃H
O
35

When the sodium salt of (±)-10-camphorsulfonic acid (35) was fused with potassium hydroxide, (±)-campholenic acid (34) was produced in 78% yield. Esterification of 34 using potassium carbonate and methyl iodide in acetone gave the corresponding ester 40 in 98% yield. The structure of the ester was readily established from its spectral data. The ir spectrum showed the ester absorption band at 1748 cm^{-1}. In the nmr spectrum, the singlets at δ 3.68, 1.62, 0.98 and 0.78 were assigned to the methyl ester, vinylic methyl and gem-dimethyl respectively. The broad multiplet at δ 5.22 was readily assigned to the vinylic proton. The mass spectrum displayed a molecular ion peak at m/z 182.1305 which was consistent with the molecular formula $C_{11}H_{18}O_2$ which was further confirmed by the elemental analysis.



40

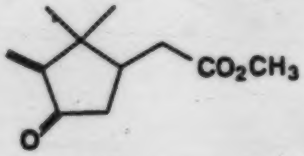
Photooxygenation of ester 40 in methanol using methylene blue as a photosensitizer[84] followed by reduction of the resulting hydroperoxides with sodium borohydride gave an epimeric mixture of allylic alcohols 41 in 66% yield. In the ir spectrum characteristic



41

absorption bands were observed at 3440 (alcohol), 3106, 1655 (olefin) and 1748 cm^{-1} (ester). The ratio of the two epimeric alcohols was found to be approximately 7:3 as determined by nmr spectrum which displayed two pairs of methyl singlets, one at δ 1.12 and 0.82 and the other at δ 1.02 and 0.92. In agreement with the structural assignment, broad singlets at δ 5.12 and 4.92 for the vinylic protons and a singlet at 3.66 for the methyl ester were also observed. The methine proton adjacent to the hydroxyl group appeared at δ 4.95 as a multiplet. The molecular ion peak at m/z 198.1232 in the mass spectrum confirmed the chemical formula of $C_{14}H_{24}O_3$.

Swern oxidation[85] of the mixture of the epimeric alcohols **41** with oxalyl chloride, dimethyl sulfoxide, and triethylamine gave enone **42** in 85% yield. The ir spectrum



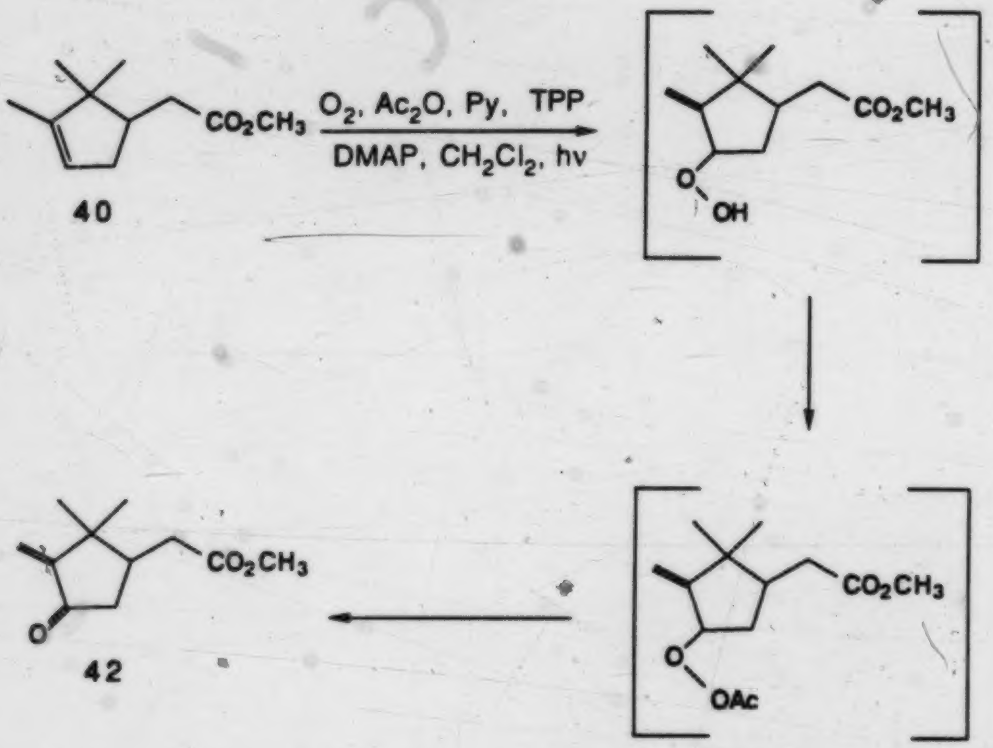
42

showed absorptions at 1748 cm^{-1} for the ester group, 1729 cm^{-1} for the unsaturated ketone and 1634 cm^{-1} for the carbon-carbon double bond. The nmr spectrum displayed two broad singlets at δ 5.98 and 5.20 for the enone protons. Two doublets of doublets appeared at δ 2.54 (1H, J = 18, J' = 7 Hz) and 2.06 (1H, J = 18, J' = 11 Hz) due to protons α to the ketone carbonyl. The singlets at δ 1.22 and 1.00 were due to the gem-dimethyl group. The molecular formula $C_{11}H_{16}O_3$ was verified by the presence of a molecular ion peak at m/z 196.1305 in the mass spectrum and by the elemental analysis.

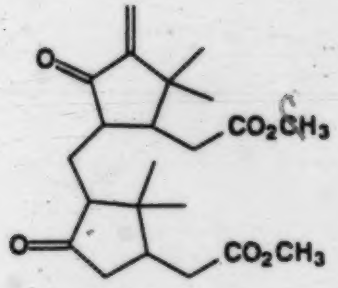
Later, it was also found that enone **42** could be prepared in one step from **40** using the procedure of Mihelich and Eickhoff.[86] Ester **40** was photoxygenated in dichloromethane in the presence of pyridine, acetic anhydride and 4-dimethylaminopyridine using 5,10,15,20-tetraphenyl-21H,23H-porphine (TPP) as a photosensitizer. Under these conditions enone **42** was obtained directly in 76% yield. As shown in Scheme XI the formation of **42** could be rationalized by involking the intermediacy of a peracetate which gave rise to the observed product upon elimination of a molecule of acetic acid.

With enone **42** in hand we set out to investigate the incorporation of a propionate unit in order to prepare a compound of type **38**. The Michael addition of enone **42** to

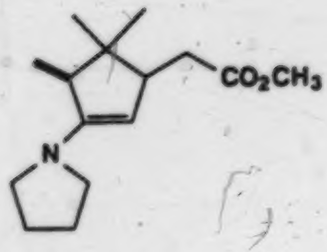
Scheme XI


CO2CH3
O2, Ac2O, Py, TPP
DMAP, CH2Cl2, hν
40
CO2CH3
O
OH
CO2CH3
O
OAc
CO2CH3
O
42

ethyl acrylate was examined first under a variety of conditions. Unfortunately, in no case was the desired Michael adduct formed and the only product observed was compound **43** resulting from dimerization of the starting material via a Michael reaction. The structure of the dimer was readily identified. The ir spectrum showed a broad carbonyl band at 1734 cm^{-1} and an absorption at 1638 cm^{-1} indicative of an olefin. The nmr spectrum displayed two one-proton singlets at δ 5.98 and 5.28 characteristic



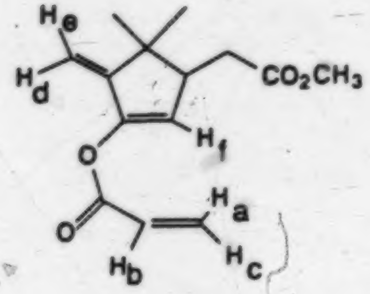
43



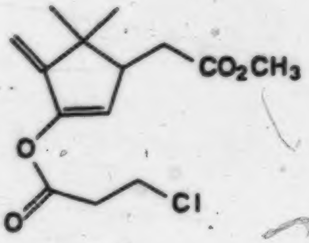
44

of the geminal protons of the methylidene group. The methoxy groups appeared at δ 3.76 and 3.72 as singlets. Four additional methyl singlets were observed at δ 1.26, 1.18, 1.03 and 0.96. The mass spectrum showed a molecular ion peak at m/z 392.2646 consistent with molecular formula $C_{22}H_{32}O_6$. Attempted alkylation using enamine **44**, which was prepared by treatment of enone **40** with pyrrolidine and a catalytic amount of p-toluenesulfonic acid in refluxing benzene, was equally unsuccessful, resulting in the formation of a complex mixture which could not be characterized.

In the alternative approach to the preparation of compound **38**, formation of enol ester **45** was attempted. Claisen rearrangement of this compound in the presence of an alcohol is expected to give the desired diester **38**. Thus, enone **42** was treated with sodium acetate in acryloyl chloride at reflux for 24 h. Three compounds, two neutral and one acidic, were produced. The neutral compounds were readily identified as the desired enol ester **45** (18% yield) and the corresponding chloride **46** (9% yield). The

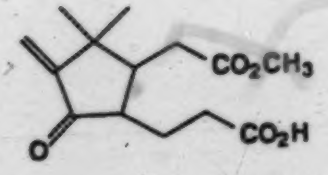


45



46

former showed, in the ir spectrum, ester absorptions at 1737 cm^{-1} and double bonds at 1630 and 1600 cm^{-1}. The nmr spectrum displayed signals at δ 6.54 (dd, H_a, J = 18 Hz, J' = 2 Hz), 6.23 (dd, H_b, J = 18 Hz, J' = 11 Hz) and 5.97 (dd, H_c, J = 11 Hz, J' = 2 Hz) for the vinylic protons of the α,β-unsaturated ester. The other vinylic protons appeared at δ 4.92 (H_d), 4.73 (H_e) and 5.92 (br., H_f) as singlets. The singlets at δ 1.22 and 1.04 were observed for the gem-dimethyl group. The mass spectrum showed a molecular ion peak at m/z 250.1202 corresponding to the molecular formula $C_{14}H_{18}O_4$. The chloro compound **46** showed absorption bands at 1769 (enol ester), 1738 (ester), 1628 and 1602 cm^{-1} (olefin) in the ir spectrum. The nmr spectrum showed one-proton singlets at δ 5.92, 4.94 and 4.73 for the vinylic protons. The signal at δ 3.84 (t, 2H, J = 7 Hz) was due to the methylene protons adjacent to the chlorine atom. The _gem_-dimethyl group appeared at δ 1.20 and 1.02 as singlets. The mass spectrum gave a molecular ion peak at 286.0972, 288.0964 consistent with molecular formula $C_{14}H_{19}O_4Cl$. The acidic material, which was produced in 57% yield, was initially thought to be the desired compound **47** resulting from concomitant Claisen rearrangement of acylation product **45**. This acid turned out to be the hydrolyzed Diels-Alder adduct between acryloyl chloride and enone **42**. Esterification with potassium carbonate and methyl iodide in acetone afforded the corresponding methyl ester **48**, which showed in the ir spectrum a strong carbonyl absorption at 1737 cm^{-1} (ester) and an olefinic absorption at 1640 cm^{-1}. The absence of any vinylic protons in the nmr spectrum strongly suggested the structure to be **48**. This was in accord with the



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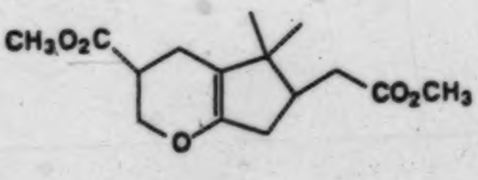
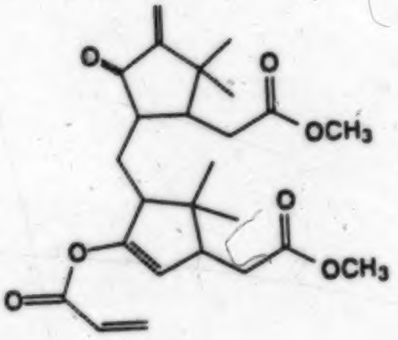


48

appearance of a pair of doublets of doublets at δ 3.74 ($J = 8$, $J' = 5$ Hz) and 3.72 ($J = 8$, $J' = 3$ Hz) due to the methylene protons adjacent to the enol ether oxygen as well as four methyl singlets at δ 3.70, 3.65, 0.92 and 0.75. The overall incorporation of a methyl acrylate moiety was further confirmed by the mass spectrum in which a molecular ion peak was found at m/z 282.1469. The structure of this compound was further verified by ^{13}C nmr spectrum which showed the signals at δ 173.93, 171.71, 121.29 and 116.54, clearly indicating the presence of two ester carbonyls and a double bond. Although the spectral data indicated that the Diels-Alder adduct was a single stereoisomer, the stereochemistry could not be deduced unambiguously.

When the above enol ester formation was carried out in refluxing acryloyl chloride using potassium carbonate as the base, the formation of the Diels-Alder product **48** was completely suppressed and the enol ester **45** was isolated in 30% yield along with a 12% yield of **46**. In this case a large amount of unreacted material was recovered even after a long reaction period of time. Further improvement of the reaction was effected by increasing the reaction temperature. Thus, treatment of enone **42** with acryloyl chloride and potassium carbonate in refluxing toluene over an extended period (72 h) gave rise to enol ester **45** and chloride **46** in 53% and 6% yield respectively. Under these conditions, two new compounds were also formed in small quantities. Structures **49** and **50** were tentatively assigned to these compounds mainly on



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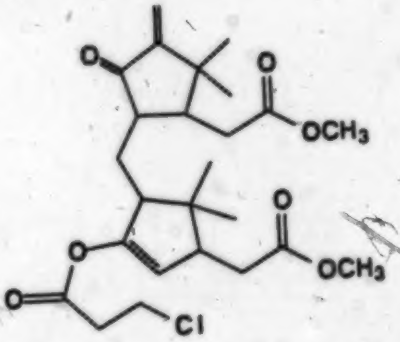
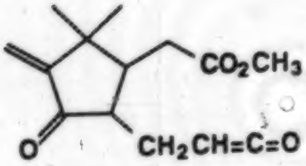


50

the basis of the mass spectra which showed molecular ion peaks at m/z 446.3507 and m/z 482.2385. Further improvement on the formation of the desired enol ester **45** was attempted without success. When sodium carbonate was used as a base similar results were obtained, while a complex mixture was produced on carrying out the reaction in refluxing xylene.

With enol ester **45** in hand, we turned our attention to the Claisen rearrangement which could in principle lead to the formation of ketene **51**. Furthermore, when the reaction is carried out in the presence of an alcohol the corresponding ester is expected. Thus, enol ester **45** was subjected to rearrangement in refluxing toluene-methanol and xylene-methanol. Under these conditions, however, the starting material was recovered intact. On the other hand, when compound **45** was heated in refluxing xylene-pentanol, the desired diester 52 was formed. However, the yield was found to be very low. After 48 h, only 16-33% yield of 52 was produced with the balance of material being mainly the unreacted starting compound. Diester 52 showed in the ir spectrum a broad carbonyl band centered at 1738 cm^{-1} and an absorption at 1642 cm^{-1} indicative of an olefin. The nmr spectrum displayed two one-proton singlets at δ 6.40 and 5.22 characteristic of geminal protons of the methylidene group. The triplet at δ 3.97 integrating to two protons was attributed to the methylene protons adjacent to the oxygen. The methyl ester protons appeared as a singlet at δ 3.70. Two other methyl singlets and a methyl triplet (J = 7 Hz) were obtained at



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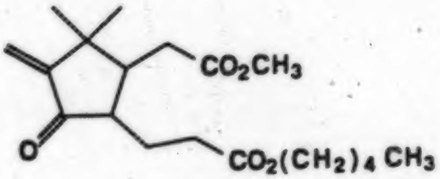
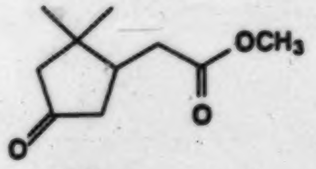


52

δ 1.20, 1.02 and 0.92 respectively. The mass spectrum showed a molecular ion peak at m/z 338.2093 indicating the molecular formula of $C_{19}H_{30}O_5$. Attempts to improve the yield of diester **52** by increasing the reaction time and by the use of xylene and cyclohexanol were unsuccessful. Surprisingly, no reaction was observed using the latter combination. Although the formation of the desired diester **52** could be effected via the Claisen rearrangement, the best yield obtained was only 33% from enol ester **45**. This yield was not synthetically useful and an alternative route was sought.

In view of the problems associated with the methylidene group in compound **42**, we decided to remove it prior to further elaboration. The cleavage of the methylidene group was initially attempted via a combination of hydration and retro-Aldol reaction. In practice, this proved not to be viable. Under no conditions applied, could the desired keto ester **53** be generated.



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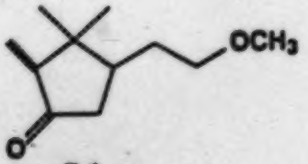

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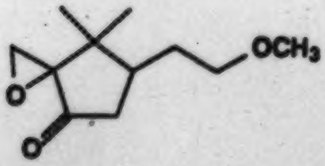

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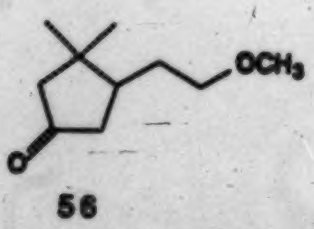
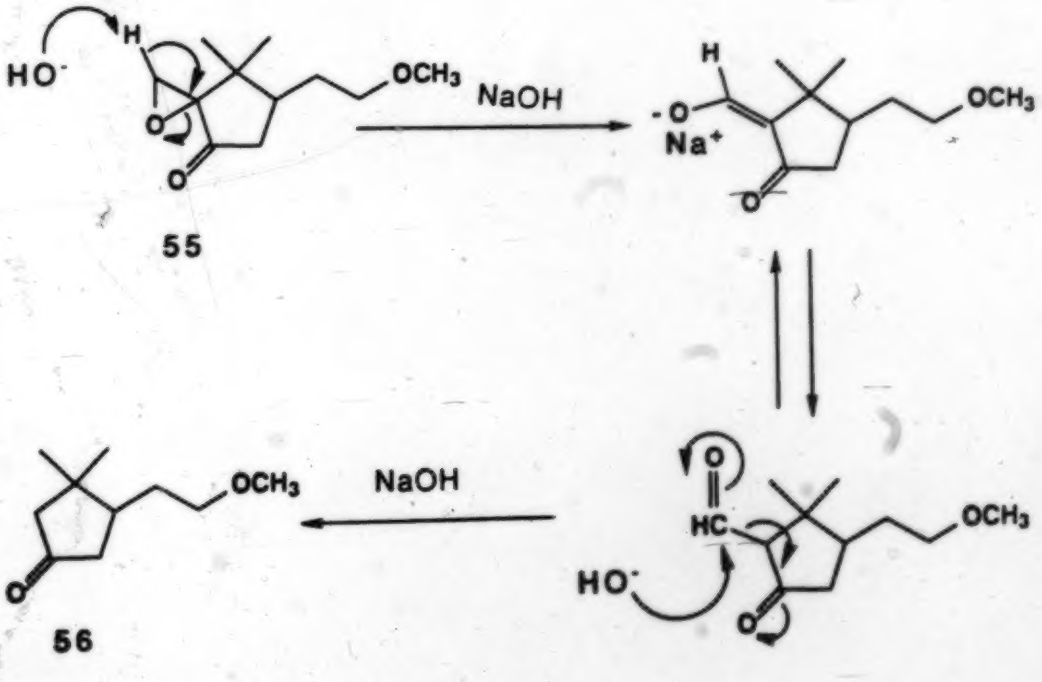


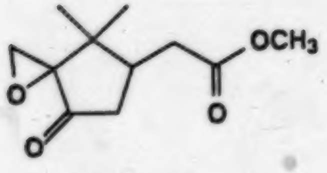
56

While this work was in progress, the elimination of the methylidene group of a closely related system **54** was investigated in our laboratory.[87] It was found that compound **54** could be converted to the corresponding epoxides **55** by treatment with hydrogen peroxide and lithium hydroxide in methanol. Interestingly, when the mixture of the epimeric epoxides was heated with sodium hydroxide in methanol at reflux, keto ether **56** was produced in 68% yield, presumably via a mechanistic pathway illustrated in Scheme XII. This procedure was

Scheme XII



applied to compound **42**. On addition of a premixed solution of aqueous lithium hydroxide (0.2 eq.) and 30% hydrogen peroxide to a methanolic solution of enone **42** at 0°C followed by warming up to room temperature, a mixture of epimeric epoxides (**57**) (1:1) was formed in 86% yield after 3 h. The sequence of addition was found to be crucial to the success of the epoxidation. Sequential addition of lithium hydroxide and hydrogen peroxide without premixing gave rise to a large amount of methoxy ketone **58** as a by-product, apparently produced by the 1,4-addition of methoxide to the enone moiety. The nmr spectrum of epoxides



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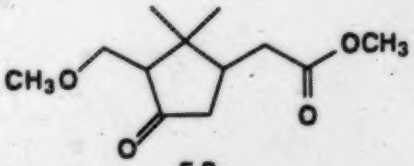
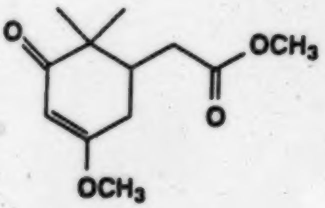


58

57 displayed protons on the epoxide ring at δ 3.15 and 2.85 as doublets with a coupling constant of 6 Hz each for one isomer and at δ 3.00 and 2.96 also as doublets (J = 6 Hz) for the other isomer. A pair of singlets at δ 3.76 and 3.72 integrating to three protons each was due to methyl ester groups. Gem-dimethyl groups appeared as singlets at δ 1.04, 0.98, 1.00 and 0.94. The ir spectrum showed absorption bands at 1742 (five membered ring ketone) and 1738 cm^{-1} (ester). A molecular ion peak at m/z 212.1043 was consistent with molecular formula $C_{11}H_{16}O_4$.

Heating a solution of epoxides **57** and sodium hydroxide (2.5 eq.) in methanol-water (10:1) at reflux for 2 to 3 days afforded an acidic material which was esterified immediately with potassium carbonate and methyl iodide in acetone. Two products were isolated, the desired keto ester **53** in 18-27% yield and a by-product 59 in nearly equal amount. The ir spectrum of **53** showed an absorption band at 1740 cm^{-1} due to the five membered ring ketone and the ester. The nmr spectrum displayed a singlet at δ 2.14 for the neopentyl protons adjacent to the carbonyl. Three additional singlets were observed at δ 3.70, 1.18, and 0.92 for the methyl groups. The mass spectrum showed a molecular ion peak at m/z 184.1097 corresponding to the molecular formula $C_{10}H_{16}O_3$. The

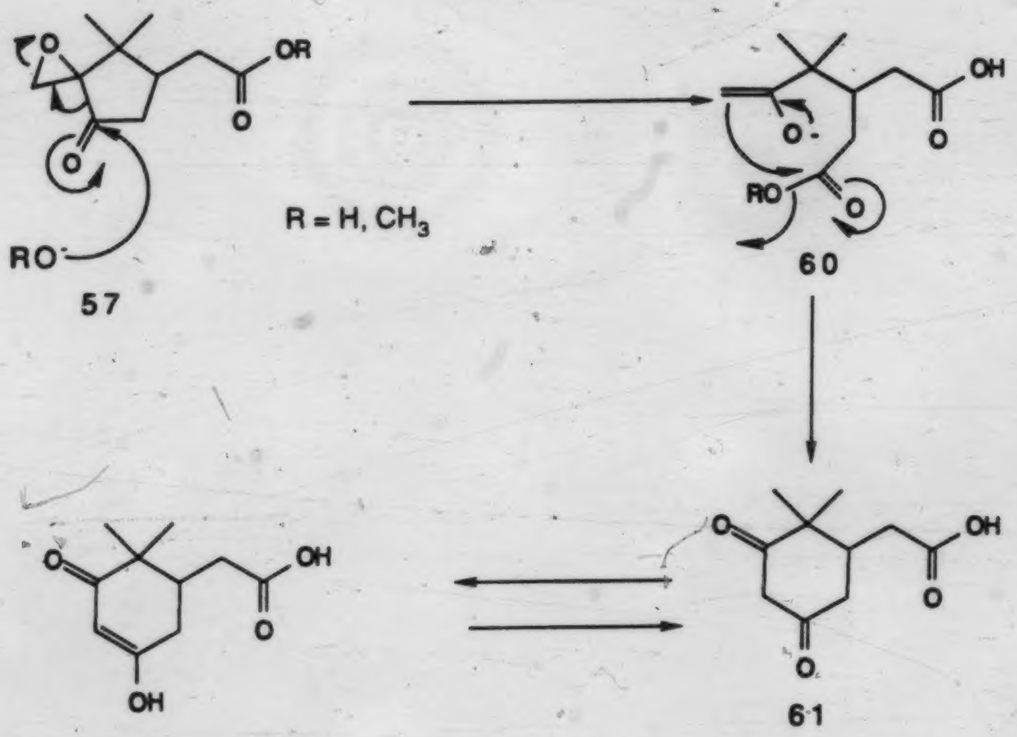


59

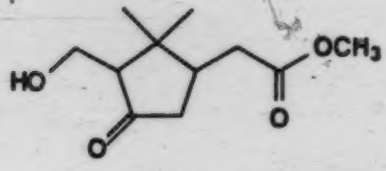
major by-product was identified as the rearranged keto ester **59** on the basis of the following spectral data. The ir spectrum showed diagnostic absorption bands at 1735 (ester), 1710 and 1620 cm^{-1} (β-methoxy α,β-unsaturated ketone). The nmr spectrum showed a vinyl proton as a singlet at δ 7.15. Four methyl signals appeared as sharp singlets at δ 3.86 (methyl enol ether), 3.72 ($-COOCH_3$), 1.32 and 1.04 (gem-dimethyl). Exact mass measurement revealed a molecular weight of 226.1204 in agreement with the required molecular formula of $C_{12}H_{18}O_4$. The formation of compound **59** could be attributed to a 1,3-glycol type cleavage (**57** → **60**), followed by a Claisen-type cyclization (**60** → **61**) as shown in Scheme XII. Methylation of diketo acid **61** would lead to the observed product **59**.

In order to improve the transformation of epoxides **57** to keto ester **53**, several modifications were examined. When the reaction was carried out at 0°C, keto ester **59** was isolated as the only product after esterification. The best results were obtained when the reaction was performed in the following manner. To the epoxides **57** in refluxing methanol, an aqueous solution of sodium hydroxide in methanol was added. After _ca_. 3 days and the ensuing esterification, the desired ester was formed in 54% yield along with a 20% yield of the rearranged

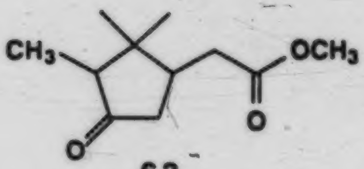
Scheme XIII



product 59. Other attempts were also made to effect the transformation of epoxides 57 to 53. It was envisaged that zinc reduction of 57 could lead to the β-hydroxy ketone 62 which might then undergo retro-aldol reaction to give ketone 53. Unfortunately, zinc reduction of epoxides 57 in refluxing acetic acid gave mainly methyl ketone 63 (33% yield) and only a small amount of the desired hydroxy ketone 62 (14% yield). The latter showed in the ir



62

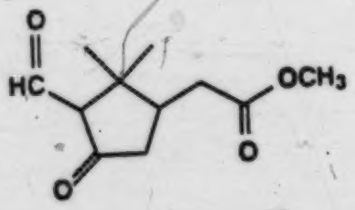


63

spectrum broad bands centered at 3540 cm^{-1} for the hydroxyl group and 1740 cm^{-1} for the ketone and ester. The mass spectrum displayed a molecular ion peak at m/z 214.1206 which was consistent with molecular formula $C_{11}H_{18}O_4$. The nmr spectrum showed a methoxy singlet at δ 3.70 which was partially superimposed with the multiplet centered at δ 3.72 for the methylene protons adjacent to the hydroxyl group. Only a pair of singlets appeared at δ 1.06 and 0.84 for the gem-dimethyl group suggesting a single stereoisomer. The stereochemistry however could not be readily assigned on the basis of the available data. The methyl ketone **63** was probably produced by dehydration of compound **62** followed by further reduction of the resulting enone (i.e. **42**). The absorption at 1739 cm^{-1} in the ir spectrum was due to ketone and ester functional groups. The nmr spectrum displayed a quartet (J = 8.5 Hz) at δ 2.04 for the methine proton adjacent to the carbonyl group. The doublet (J = 8.5 Hz) at δ 0.96 was due to the newly introduced methyl group. Other methyl signals were observed at δ 3.70, 1.12 and 0.85, each as a singlet. The mass spectrum showed a molecular ion peak at m/z 198.1262 confirming the molecular formula.

When the zinc reaction was carried out in refluxing benzene, an improved yield (38%) of hydroxy ketone **62** was realized along with recovery of an approximately equal amount of the starting material. The retro-aldol reaction of the hydroxy ketone **62** was examined using sodium methoxide in refluxing benzene. The reaction gave rise to a complex mixture which could not be easily identified. Due to these findings the zinc reduction approach to ketone **53** was abandoned.

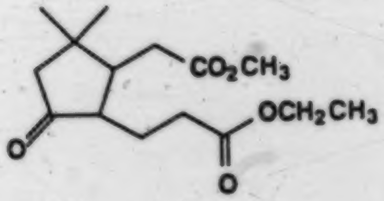
As an alternative, epoxide **57** was subjected to treatment with sodium hydride (2 eq.) in benzene at reflux, in an attempt to prepare the formyl ketone **64** which could then be deformylated to ketone **53**.



64

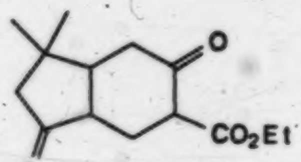
Interestingly, the latter compound was formed directly but in low yield (18%) and a substantial amount of the starting material was recovered. The yield of **53** could not be improved to a greater extent even with a larger excess of sodium hydride. Likely, the transformation was induced by the small amount of sodium hydroxide present in the reaction mixture.

For the incorporation of the required propionate side chain, keto ester **53** was subjected to Michael addition with ethyl acrylate (1.5 eq.) in 1,2-dimethoxyethane at room temperature in the presence of sodium hydride for 24 h. Good yields (83-93%) of the desired diester **65** could be obtained when less than 300 mg of the starting ketone was used. The ir spectrum of **65** displayed diagnostic absorption bands at 1739 cm^{-1} for the ester and ketone carbonyl groups. In the nmr spectrum, the ethyl group appeared at δ 4.12 (q, 2H, J = 8 Hz) and 1.32 (t, 3H, J = 8 Hz). The methylene protons α to the ketone appeared as a singlet at δ 2.18. Three methyl singlets were obtained at δ 3.72, 1.08 and 0.94. The mass spectrum showed a molecular ion peak at m/z 284.1617 indicating the



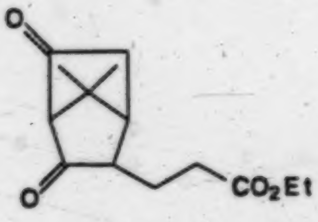
65

molecular formula $C_{15}H_{24}O_5$. Dieckmann condensation of diester **65** was effected by sodium methoxide (prepared *in situ* from methanol and sodium hydride) in refluxing



66

toluene for 24 h. The diketo ester **66** thus obtained showed in its mass spectrum a molecular ion peak at m/z 252.1201 ($C_{14}H_{20}O_4$). The ir spectrum showed absorptions at 1740 (cyclopentanone), 1656 and 1601 cm^{-1} (enolized β-keto ester). The nmr spectrum displayed a chelated enol proton at δ 13.54 as a singlet. The signals at δ 4.08 (q, 2H, J = 8 Hz) and 1.28 (t, 3H, J = 8 Hz) were due to the ethyl group of the ester. The compound appeared to be a single stereoisomer as only one set of three singlets was observed at δ 2.18, 1.22 and 1.00. The former could be attributed to the methylene group adjacent to the five membered ketone carbonyl and the other signals were due to the gem-dimethyl group. Since subsequent transformation employs conditions under which enolization of the five-membered ring ketone would also be effected, the ring junction stereochemistry of compound **66** was not determined.



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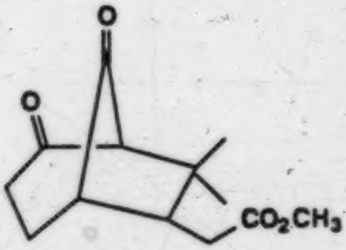

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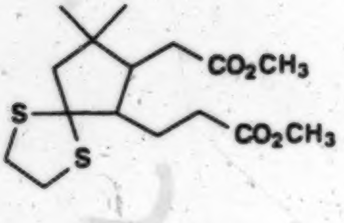
In principle under the described conditions keto diester **65** could also undergo other modes of cyclization leading to compounds **67** and **68**, involving enolate ion of the ketone carbonyl. To confirm the structural assignment, keto ester **66** was prepared in an unambiguous manner as follows. Thiolketalization of **65** with 1,2-ethanedithiol and boron trifluoride etherate in methylene chloride at room temperature for 6 h gave rise to the corresponding thiolketal **69** in 82% yield. The nmr spectrum showed a multiplet at δ 3.33 and integrating to four protons for the methylene protons of thiolketal group. The mass spectrum showed a molecular ion peak at m/z 360.1432 indicating the chemical formula $C_{17}H_{28}S_2O_4$. The thiolketal **69** was subjected to Dieckmann condensation in 1,2-dimethoxyethane using sodium hydride and methanol and a catalytic amount of potassium hydride. After 5 h at reflux, β-keto ester **70** was isolated in 78% yield. The ir spectrum showed an intense and broad absorption band at



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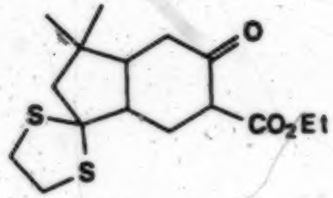
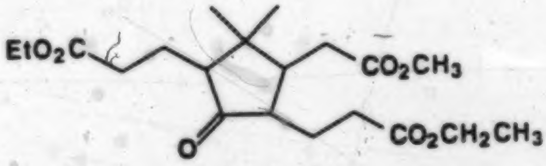


70

1735 cm^{-1} and two weak bands at 1655 and 1610 cm^{-1} indicating the compound was mainly in the ketone form. The nmr spectrum displayed a quartet at δ 4.10 and a triplet at δ 1.27 for the ethyl group of the ester. A multiplet at δ 3.27 was due to the methylene protons adjacent to the sulfur atoms. A molecular ion peak at m/z 328.1169 in the mass spectrum verified the chemical formula of $C_{16}H_{24}S_2O_3$. Dethiolketalization[88] of keto ester **70**, effected by mercuric chloride and calcium carbonate in refluxing aqueous acetonitrile for 4 h, gave keto ester **66** (45% yield) identical in all respects with the one obtained previously.

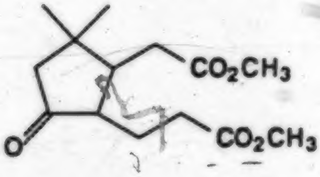
While the sodium hydride induced Michael addition of keto ester **53** to ethyl acrylate (vide supra) proceeded smoothly when small amount of material was used, for reasons that remain unknown, the yield of product decreased substantially when reaction was scaled up. For instance, when 76 mg of keto ester **53** was used, a 93%

yield of diester **65** was obtained. The yield dropped to 83% when 216 mg of compound **53** was applied. When the Michael reaction was attempted in gram-scale under the described conditions at room temperature in 1,2-dimethoxyethane, it was consistently observed that the reaction ceased after the initial formation of the product. In an attempt to promote the reaction by heating the mixture to reflux, extensive alkylation occurred and triester **71** was isolated in 76% yield as the only product.



71

In order to circumvent this problem the use of lithium diisopropylamide as the base was investigated. When keto ester **53** was treated with lithium diisopropylamide (prepared _in situ_ from diisopropylamine and methyllithium) at -78°C in tetrahydrofuran followed by addition of ethyl acrylate, the desired product **65** was formed after 1 h at -78°C and 4 h at room temperature. The yield was 86% when 303 mg of the starting material was used. Disappointingly, when the reaction was carried out with _ca_. 500 mg of the material, the yield of the desired product dropped again rapidly to ca. 40% along with substantial recovery of the starting material. After some further preliminary investigation, it was observed, to our delight, that the reaction took a different course when performed in the presence of a small amount of hexamethylphosphoramide. In addition to the formation of diesters 72 (methyl acrylate was used as the reagent), subsequent Dieckmann cyclization occurred simultaneously to give a single keto ester 73 existing completely in the corresponding enol form. The best results were obtained when keto ester 53 was subjected to treatment with lithium diisopropylamide (1.1 eq.) in tetrahydrofuran in the presence of hexamethylphosphoramide (1.1 eq.) at -78°C followed by addition of methyl acrylate (1.2 eq.) at -40°C and by allowing the mixture to react at 0°C for 5 h. Under these conditions, β-keto ester 73 was produced in 48% yield, along with 23% of diesters 72 (7:3) and 18% of by-product 74. Diesters 72 could readily be cyclized to provide an additional amount of β-keto ester 73 (94%



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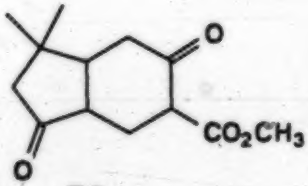

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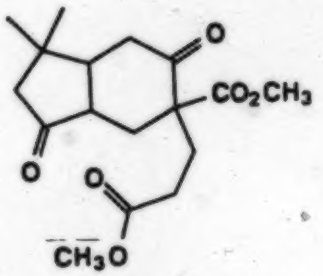
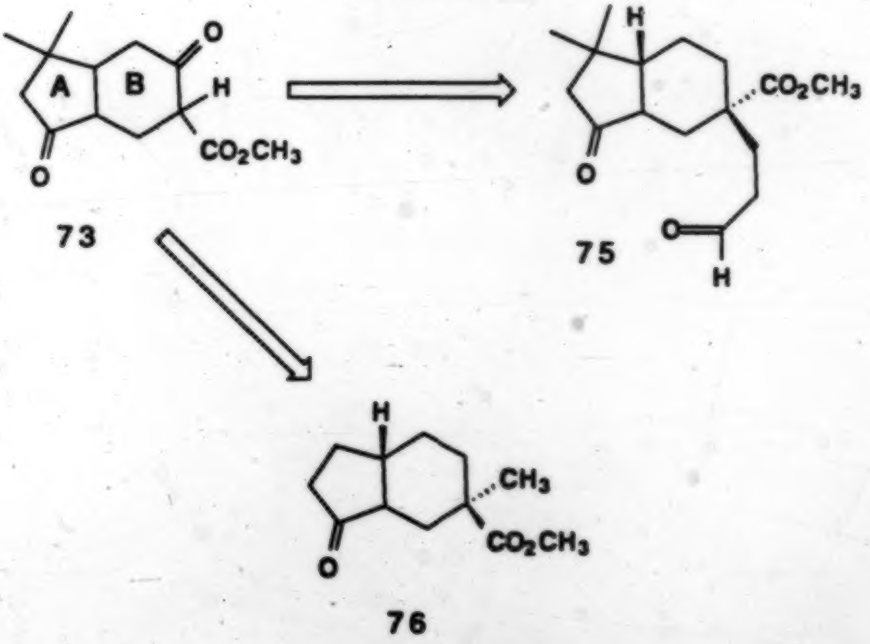


74

yield) when further exposed to lithium diisopropylamide in tetrahydrofuran at room temperature for 6 h. The ir spectrum of diesters 72 and keto ester 73 were found to be similar to those obtained for the corresponding ethyl compounds 65 and 66. In the mass spectra, each showed a molecular ion peak with fourteen mass units less, while in the nmr spectrum, the ethyl ester signals observed for 65 and 66 were replaced by the methoxy singlets (four singlets at δ 3.75, 3.72, 3.70, 3.68 for 72 and a singlet at δ 3.77 for 73 . Diketo ester 74 showed in the ir spectrum a broad band at 1739 cm^{-1} for the esters and the five membered ring ketone. The absorption at 1713 cm^{-1} was assigned to the six membered ring ketone. In the nmr spectrum five singlets appeared at δ 3.75, 3.65 (methoxy groups), 2.30 (methylene protons of the cyclopentanone moiety), 1.18 and 0.92 (gem-dimethyl). The mass spectrum showed a molecular ion peak at m/z 324.1573 in agreement with the molecular formula $C_{17}H_{24}O_6$.

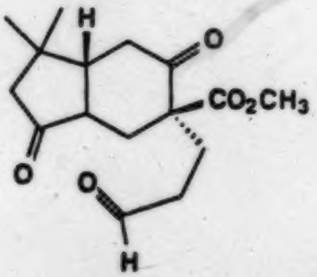
Concurrent to the studies described immediately above, the alkylation of keto ester 53 with β-bromopropionate was also examined. Sequential treatment of 53 with near stoichiometric amounts of lithium diisopropylamide and methyl 3-bromopropanoate in tetrahydrofuran in the presence of hexamethylphosphoramide (1.0 eq.), initially at -78°C then at room temperature for 10 h gave rise to keto ester 73 and diesters 72 in ca. 1:2 ratio and in a total yield of 66%. Both this reaction and the Michael reaction using hexamethylphosphoramide were shown to be reproducible regardless of the reaction scale. Of these two procedures the latter is preferred since it provides directly a higher yield of the cyclic material.

Scheme XIV



For the construction of the C ring from compound **73**, two approaches are readily conceivable (Scheme XIV). In one approach the ester group is to be used as the angular methyl group and a suitable substituent will be introduced (**73** → **75**) to facilitate the C ring formation. In the other, a methyl group will be incorporated (**73** → **76**) and the ester moiety be used as part of ring C. The viability of these approaches will depend on the stereochemical outcome of the alkylation step (i.e. **73** → **75** and **73** → **76**). Both of these approaches were examined and the results are as follows.

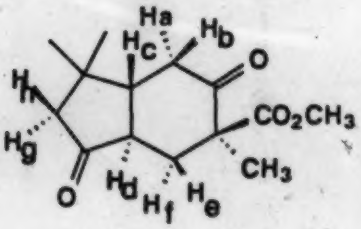
Compound **73** was found to undergo both methylation with methyl iodide and Michael addition with acrolein. Treatment of **73** with ca. one equivalent each of acrolein and 1,4-diazabicyclo[2.2.2]octane in 1,2-dimethoxyethane at room temperature for 4 h gave keto aldehyde **77** in 90%



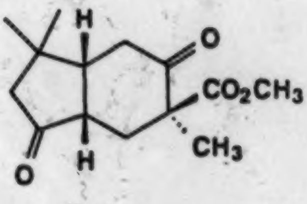
77

yield. The ir spectrum of **77** showed absorption bands at 2860, 2720 (aldehyde), 1740 (ester and cyclopentanone) and 1713 cm^{-1} (aldehyde and cyclohexanone). The nmr spectrum displayed a broad singlet at δ 9.66 for the aldehyde proton. Sharp methyl singlets were observed at δ 3.72 (methyl ester), 1.08 and 1.02 (gem-dimethyl group). The regiochemistry of the Michael adduct was substantiated by the presence of a two-proton singlet at δ 2.18 assigned to the cyclopentanone methylene group and the disappearance of the signal corresponding to the enol proton. The mass spectrum displayed a molecular ion peak at m/z 294.1466. The spectral data also suggested that the compound was a single stereoisomer. The indicated stereochemistry was deduced from the results obtained for the subsequent methylation reaction of **73** (see below). Since this compound likely possesses the incorrect stereochemistry, further elaboration was not carried out.

The initially attempted methylation, using sodium hydride as a base, resulted in complete recovery of the starting material. When potassium hydride was employed, the reaction of **73** with methyl iodide in tetrahydrofuran at room temperature occurred to give the desired methylation product in 82% yield. However, dimethylation also occurred to the extent of 8-10%. This side reaction could be suppressed completely by the use of potassium carbonate as the base and acetone as the solvent.[89] A 82% yield of two products was obtained in the ratio of 2:1. These compounds were not readily separable. However, by fractional crystallization the major component (m.p. 75-76°C, petroleum ether-ethyl acetate) could be isolated in pure form. Treatment of this compound with potassium carbonate in refluxing acetone for 24 h gave rise to a new mixture consisting of the starting material and the 'minor' compound in ca. 1:3 ratio with the latter predominating. These observations clearly indicated that the two products produced by the methylation reaction were isomeric at an epimerizable center(s). Since the structure **78** could be assigned to the major isomer on the basis of the spectral data, it follows that the minor isomer should possess the structure **79**. Diketo ester **78** showed absorption bands at 1741 and 1710 cm^{-1} in the ir spectrum due to the ester and ketone functionalities. The



78



79

mass spectrum showed a molecular ion peak at m/z 252.1363 in agreement with molecular formula $C_{14}H_{20}O_4$. The nmr spectrum displayed four methyl singlets at δ 3.74, 1.43, 1.17 and 1.07. By decoupling experiments it was possible to assign all the remaining protons as follows: δ 2.54 (dd, J = 15, J' = 5 Hz, H_b), 2.48 (dd, J = 15, J' = 13 Hz, H_a), 2.46 (ddd, J = J' = 13, J" = 5 Hz, H_d), 2.35 (dd, J = 19, J' = 2 Hz, H_g), 2.26 (t, J = 13 Hz, H_e), 2.16 (d, J = 19 Hz, H_h), 2.14 (dd, J = 13, J' = 5 Hz, H_f) and 1.90 (ddd, J = J' = 13, J" = 5 Hz, H_c).

Since both of the ring junction protons H_c and H_d appeared as a doublet of doublets of doublets with two large coupling constants of 13 Hz each and a small coupling of 5 Hz, a trans-ring junction could readily be assigned. In order to determine the stereochemistry of the remaining center, the following nOe experiments were carried out. When C_4 methyl singlet (δ 1.43) was irradiated, the doublet of doublets of doublets at δ 2.46 (H_d) and the doublet of doublets at δ 2.48 (H_a) each showed a 4% enhancement. An 8% enhancement was observed for H_f which appeared at δ 2.14 as a doublet of doublets while the doublet of doublets of doublets at δ 1.90 (H_c) was unaffected. These observations strongly suggested that the methyl group was cis to H_a H_d and H_f and trans to H_c. Consequently, the stereochemistry of compound **78** was

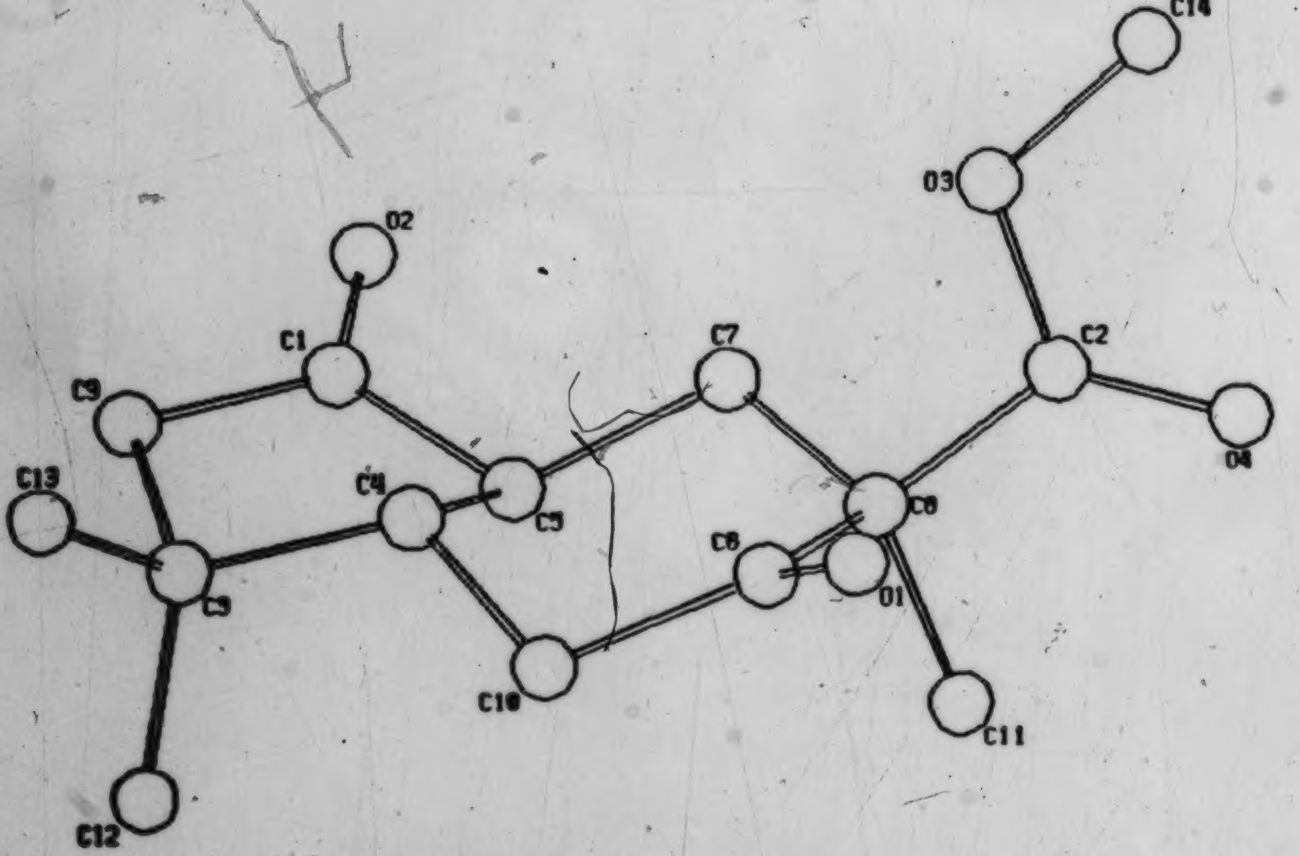
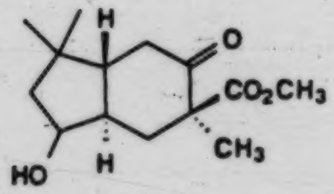

C14
O3
O2
C1
C7
C2
C9
O4
C13
C4
C5
C8
C6
O1
C3
C10
C11
C12

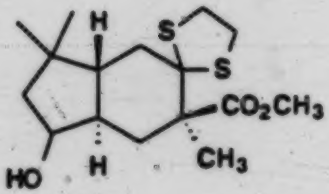
Fig.1 The three dimensonal X-ray crystallographical of structure of diketo ester 78

deduced. This assignment was further confirmed by a single X-ray diffraction analysis. A computer generated perspective drawing of this compound is shown in Fig. 1.

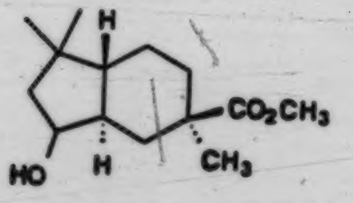
Both diketo esters **78** and **79** are synthetically useful, since they differ from each other only in stereochemistry at an epimerizable center. Since the trans compound **78** was obtained in larger quantity and in pure form, it was used for the present studies. Prior to the incorporation of ring C, the removal of the six membered ketone carbonyl was examined. In principle, this could be effected by selective reduction of the less hindered five membered ring ketone (**78** → **80**), thioketalization (**80** → **81**), desulfurization (**81** → **82**) and regeneration of the cyclopentanone (**82** → **83**). Thus, diketo ester **78** was



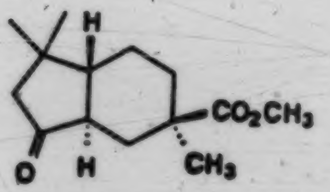
80



81

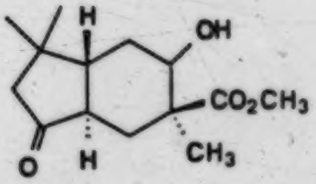


82



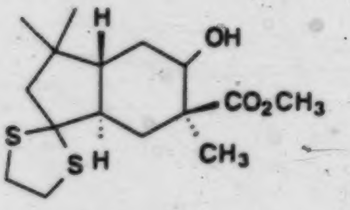
83

subjected to reduction with lithium tri-t-butoxyaluminium hydride (1.2 eq.)[61] in tetrahydrofuran at room temperature. After 12 h, the reaction was complete and two products were formed in 97% yield. To our surprise, the products were shown to be keto alcohols **84**, resulting from the selective reduction of what appeared to be the more hindered six membered ring ketone. That the cyclohexanone moiety was selectively reduced was indicated by absence of the characteristic cyclohexanone absorption at ~1710 cm^{-1} in the ir spectrum. Instead, the products displayed absorption bands at 3480 cm^{-1} for the hydroxyl group and 1740 cm^{-1} for the carbonyls. In the nmr spectrum a broad triplet appeared at δ 3.94 for the proton adjacent to the hydroxyl group. A pair of mutually coupled doublets (J = 13 Hz each) at δ 2.18 and 2.09 integrating to one proton each was assigned to the methylene group attached to the ketone carbonyl. A singlet at δ 3.74 was due to the methoxy group. Two sets of methyl

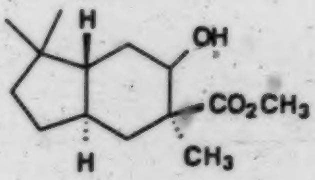


84

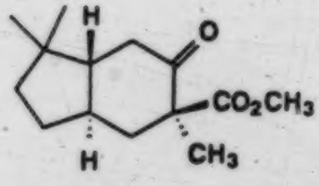
signals at δ 1.12, 1.08, 1.03 (major) and δ 1.14, 1.06 and 1.00 clearly indicated the presence of two alcohols (3:1). The mass spectrum showed a molecular ion peak at m/z 254.1522 confirming the chemical formula $C_{14}H_{22}O_4$. To verify the structural assignment, the mixture of keto alcohols **84** was converted to thioketals **85** (90% yield) using boron trifluoride etherate and 1,2-ethanethiol in dichloromethane. Dethioketalization with Raney nickel in ethanol followed by oxidation of the resulting hydroxy esters **86** with pyridinium chlorochromate[90] and sodium acetate in dichloromethane gave a single product (81% yield) which was identified as ketone **87**. It showed in the ir spectrum



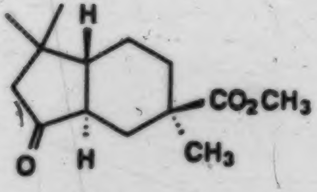
85



86



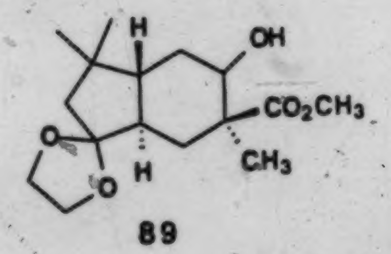
87



88

an absorption band at 1709 cm^{-1} diagnostic of a cyclohexanone moiety. The isomeric ketone **88** was not detected.

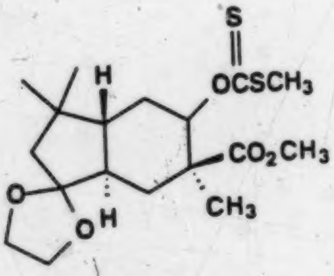
In order to prepare keto ester **88**, the mixture of keto alcohols **84** was ketalized by transketalization with 2-ethyl-2-methyl-1,2-dioxolane and a catalytic amount of p-toluenesulfonic acid in refluxing benzene. Ketals **89** were produced in 80% yield. The mixture of isomeric ketals displayed a carbonyl band at 1738 cm^{-1} and a hydroxy absorption at 3480 cm^{-1} in the ir spectrum. The nmr spectrum showed multiplets at δ 3.87 for the ketal moiety and 3.97 for the methine proton adjacent to the hydroxy group. Two sets of methyl signals for the epimeric alcohols were observed at δ 3.70, 1.22, 1.02, 0.94, and δ 3.68, 1.20, 1.00, and 0.93. The mass spectrum showed a molecular ion peak at m/z 298.1781 indicating the chemical formula $C_{16}H_{26}O_5$.



89

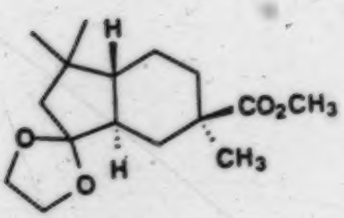
Sequential treatment of ketal alcohols **89** with sodium hydride, carbon disulfide and methyl iodide in tetrahydrofuran gave rise to the corresponding xanthates **90** in

87% yield. The ir spectrum showed a strong absorption band at 1220 cm^{-1} due to the carbon-sulfur double bond. The nmr spectrum showed a singlet at δ 2.48 and integrating to three protons for the methyl group attached to the sulfur atom.



90

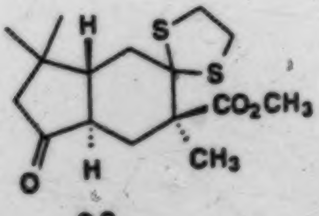
When the mixture of xanthates **90** was heated with tri-n-butyltin hydride and a catalytic amount of azobisisobutyronitrile[91] in degassed toluene under an argon atmosphere at reflux for 4 h, ketal 91 was isolated as a single compound in 78% yield. The ir spectrum displayed an absorption band at 1734 cm^{-1} for an ester. In the nmr spectrum, a multiplet at δ 3.87 was due to the protons attached to the dioxolane ring. A set of four methyl singlets appeared at δ 3.68, 1.21, 1.02 and 0.94. The mass spectrum showed a molecular ion peak at 282.1831 indicating a molecular formula $C_{16}H_{26}O_4$. Exposure of 91 to moist acetone and p-toluenesulfonic acid furnished keto ester **88** in 94% yield. The ir spectrum showed an



91

absorption band at 1741 cm^{-1} for the ester and the five membered ring ketone. The nmr spectrum displayed a singlet at δ 2.19 for the methylene protons neighboring the ketone moiety. Four other singlets were observed at δ 3.68 ($-COOCH_3$), 1.20, 1.16 and 1.04 for the methyl groups. A molecular ion peak at m/z 238.1562 in the mass spectrum confirmed the molecular formula $C_{14}H_{22}O_3$.

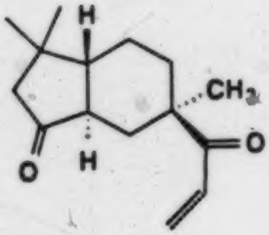
A shorter and more effective method has also been developed for the transformation of diketo ester **78** to keto ester **88**. In this two-step procedure, diketone **78** was selectively thioketalized with 1,2-ethanedithiol and boron trifluoride etherate in methylene chloride at 0°C.



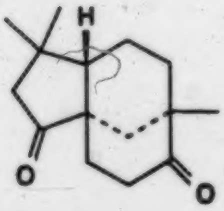
92

The ir spectrum of thioketal **92** thus obtained in 86% yield showed the absence of cyclohexanone absorption suggesting the six membered ring ketone was selectively ketalized. The mass spectrum displayed a molecular ion peak at m/z 328.1166 corresponding to the molecular formula $C_{16}H_{24}O_3S_2$. Subsequent desulfurization of **92** using Raney nickel in ethanol afforded keto ester **88** in 52% yield.

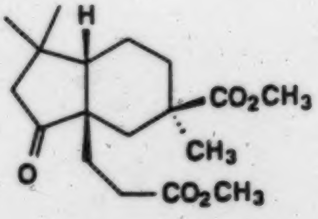
For the construction of C ring, two approaches were considered. In the first one, the methyl ester moiety in **88** was to be used as a handle for the incorporation of a suitable side chain as shown in structure **93**. Cyclization via an intramolecular Michael addition could lead to the required C ring (**93** → **94**). In the second approach, introduction of a propionate unit at the ring junction could give rise to diester **95**. Dieckmann condensation of



93

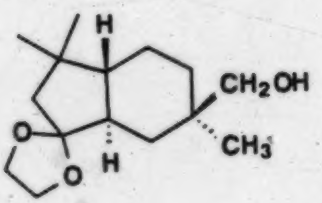


94

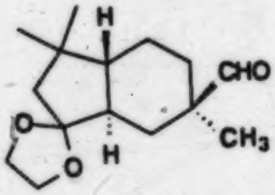


95

95 followed by decarboxylation could then provide the desired diketone **94**. Both of these approaches were attempted. Reduction of ketal **91** with sodium bis(2-methoxyethoxy)aluminium hydride in ether at room temperature for 2 h afforded hydroxy ketal **96** in 95% yield. Aldehyde **97** was prepared in 78% yield by treatment of the alcohol **96** with pyridinium chlorochromate and sodium acetate in dichloromethane at room temperature for 1.5 h. The mass spectrum of the compound suggested the molecular formula to be $C_{15}H_{24}O_3$ with a molecular ion peak at m/z 252.1536. The ir spectrum showed absorption bands at 2830, and 1739 cm^{-1} characteristic of a aldehyde moiety. The nmr spectrum displayed a broad singlet at δ 9.38 readily attributed to the aldehyde proton. Other easily identifiable signals were observed at δ 3.86 (ketal), 1.10, 1.04 and 0.96 (methyls). The conversion of the aldehyde group to a vinyl ketone required for the desired intermediate **93** proved difficult. Disappointingly, attempts to introduce the vinyl group by a Grignard

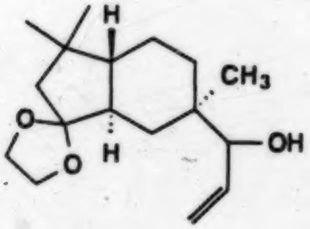


96

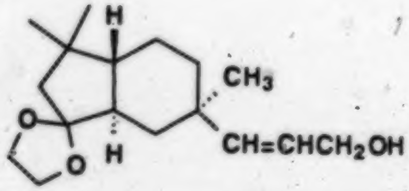


97

reaction were unsuccesful. Neither vinyllithium nor the corresponding magnesium bromide reagent reacted with aldehyde **97** at 0°C. At room temperature the reaction of **97** with vinyllithium gave a complex mixture from which no identifiable compounds could be isolated. In case of vinylmagnesium bromide, the products appeared less complex. However, the desired compound **98** could not be detected. Instead, an impure material which showed characteristics of the rearrangement product **99** was isolated in small amount.

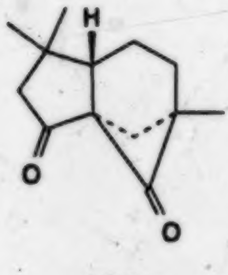


98

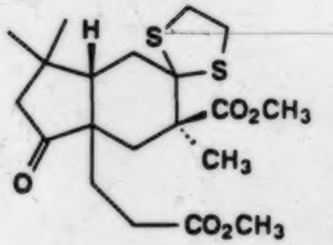


99

As a consequence of the above unsuccessful attempts, we turned our attention to the alternative approach for ring C formation. To prepare the desired compound **95**, keto ester **88** was subjected to treatment with methyl acrylate and potassium hydride in tetrahydrofuran. At 0°C no reaction occurred and the starting material was recovered intact. When the reaction was carried out at room temperature, the starting material was consumed completely after 14 h and a major product was formed. Disappointingly, the product which was found to be non-acidic and less polar than the starting material on silica gel, showed spectroscopic properties totally inconsistent with the desired structure **95**. Although the ir showed a carbonyl absorption at 1739 cm^{-1} which was expected for the five membered ketone and the ester groups, this band was rather sharp and not particularly intense. This observation coupled with the absence of any methoxy signals in the nmr spectrum suggested that the ester group had been eliminated from the starting material. The loss of a carbomethoxy was further suggested by the mass spectrum which displayed a peak at m/z 180.2230 for the composition $C_{12}H_{20}O$. At the present, we are unable to arrive at a structure for this compound which would satisfy both the available spectral data and a reasonable mechanistic pathway for its formation. One possible pathway leading to this unidentified product could involve an intra-molecular Claisen-type cyclization (**95** → **100**) as the initiating step. In order to circumvent this possible problem, the ester **92** was subjected to treatment with potassium hydride and methyl acrylate in tetrahydrofuran at room temperature. To our delight the desired addition product **101** was formed albeit in low yield (19% with 72% recovery of starting material) even after a long reaction period of 32 h. The mass spectrum which showed the molecular ion peak at 414.1535 confirmed molecular formula $C_{20}H_{30}O_5S_2$. The nmr spectrum showed two methoxy signals at δ 3.72 and 3.68. Three methyl signals appeared at δ 1.32, 1.25 and 1.14. The multiplet at δ 3.25 was due to methylene protons next to the sulfur atoms. These spectral data suggested that the adduct was formed as a single stereoisomer. However, the stereochemistry could not be unambiguously deduced. The indicated stereochemistry was tentatively assigned based on the expected addition of methyl acrylate from the less hindered side of the precursor. Currently, we are examining more suitable conditions in order to improve the yield of compound **101**.



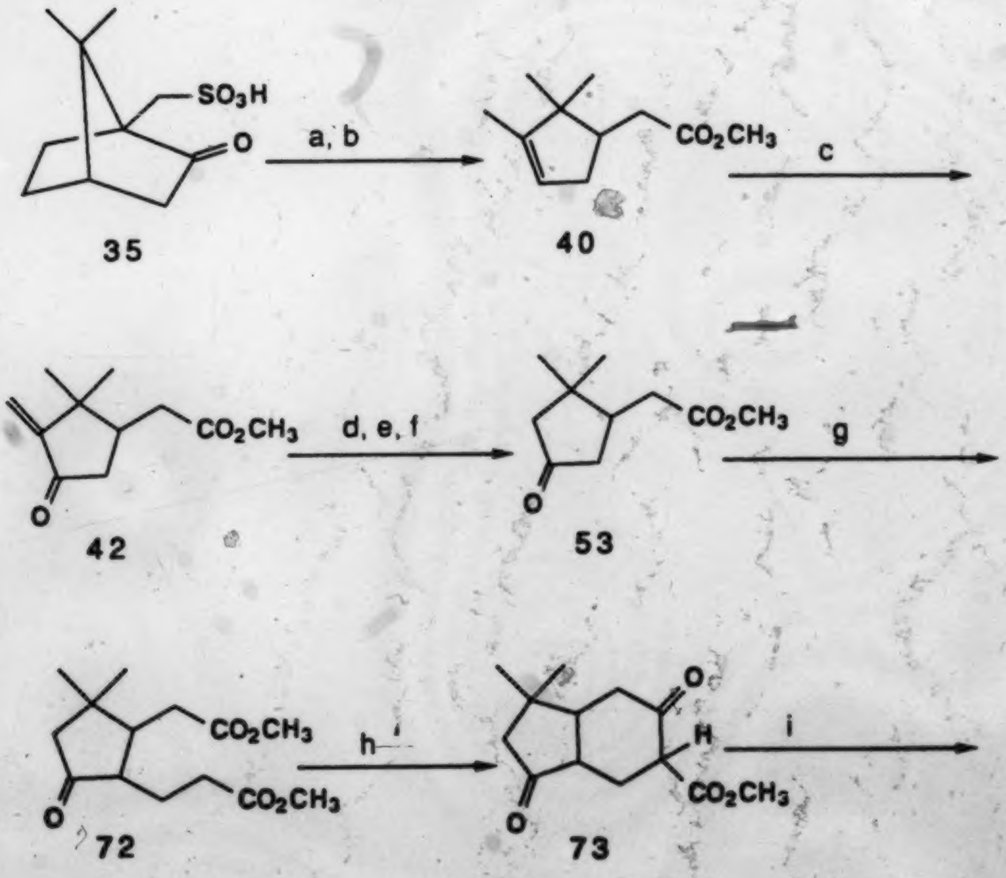
100



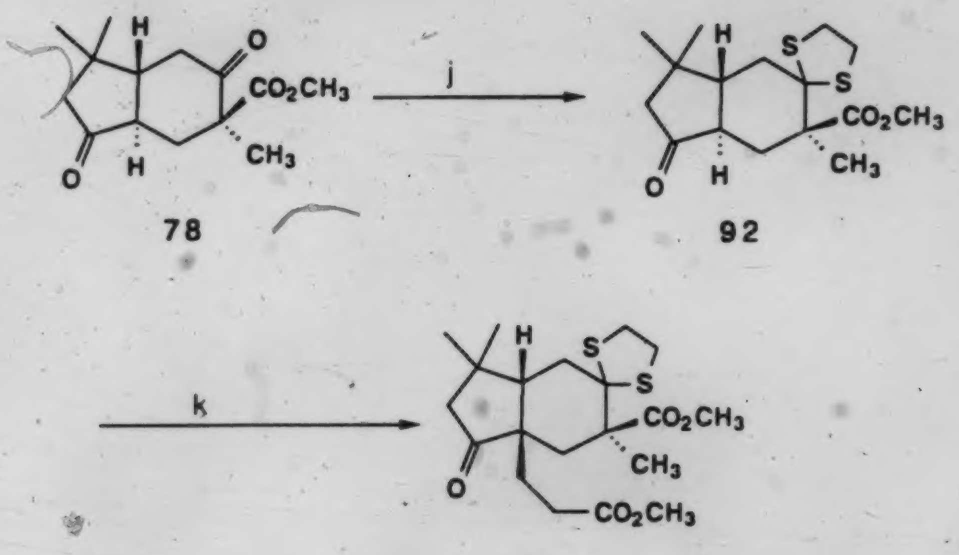
101

In conclusion, starting from 10-camphorsulfonic acid (**35**), keto diester **101** has been prepared in eleven steps by the synthetic sequence summarized in Scheme XV. This compound is considered to be a potentially useful synthetic precursor of clovane-diol (1). Desulfurization of **101** followed by Dieckmann condensation of the resulting ester **95** should lead to tricyclic compound **94** after decarbomethoxylation. This compound could be further elaborated to give the target molecule by modification of the existing functionalilties.

Scheme XV


SO₃H
O
a, b
CO₂CH₃
c
35
40
CO₂CH₃
d, e, f
CO₂CH₃
g
O
O
42
53
CO₂CH₃
CO₂CH₃
h
O
H
CO₂CH₃
i
O
O
72
73

Scheme XV (cont'd)



78

92

101

a. KOH, heat. b. K_2CO_3, CH_3I, acetone. c. O_2, Ac_2O, Py, DMAP, CH_2Cl_2, hv. d. H_2O_2 / ^-OH. e. NaOH, CH_3OH, reflux . f. K_2CO_3, CH_3I, acetone. g. LDA, -78°C to R.T. , CH_2=$CHCO_2CH_3$. h. Na^+ $^-OCH_3$, toluene, reflux. i. K_2CO_3, CH_3I, acetone. j. $BF_3 \cdot Et_2O$, $HSCH_2CH_2SH$, 0°C. k. KH, CH_2=$CHCO_2CH_3$, THF, R.T.

EXPERIMENTAL

General

For general remarks see the Experimental Section of Part I of this thesis. Carbon-13 nuclear magnetic resonance (^{13}C nmr) spectra were recorded on a Bruker WH-200 or WH-400 spectrometer and were obtained on solutions in deuterochloroform. Crystalline samples were recrystallized and liquid samples were subjected to distillation before submitting for elemental analysis.

Materials

Solvents were purified as follows: triethylamine, pyridine, diisopropylamine and acetonitrile by distillation over calcium hydride; dimethyl sulfoxide and hexamethylphosphoramide by distillation over calcium hydride at reduced pressure and stored over 3Å molecular sieves; dichloromethane was distilled over phosphorus pentoxide; acetone was treated with potassium permanganate, dried over anhydrous potassium carbonate and distilled. Boron trifluoride etherate was distilled over calcium hydride according to the procedure of Brown.[92] Other solvents were distilled by the process described in the Experimental Section of Part I. dl-Camphorsulfonic acid was obtained from Aldrich Chemical Company.

(±)-Campholenic acid (34)

A. From dl-10- camphorsulfonic acid (35)

Potassium hydroxide (242 g, 4.3 mol) was fused in a porcelain dish. The heat source was removed and immediately powdered dl-10-camphorsulfonic acid (100 g, 0.43 mol) was added slowly with vigorous stirring (the reaction is exothermic) over a period of 25 min. The colour of the molten mixture was chocolate brown. The molten mass was allowed to cool to room temperature and then dissolved in water (500 mL). The resulting solution was washed with dichloromethane (3 x 300 mL) and the aqueous fraction acidified with ice-cold 6 N aqueous hydrochloric acid. The acidified solution was extracted with dichloromethane (3 x 200 mL). The combined organic extract was dried, filtered and concentrated. The crude residue was distilled to give pure acid **34** (52 g, 71% yield): b.p. 87-89°C/0.5 torr; ir 3500 (acid) and 1719 cm^{-1} (carbonyl); nmr δ 10.90 (br, s, 1H, $-CO_2H$), 5.20 (m, 1H, -CH=), 1.60 (br, s, 3H, $CH_3-\overset{|}{C}=$), 0.99 (s, 3H, $-CH_3$) and 0.81 (s, 3H, $-CH_3$); ms M^+ 168.1142 (calcd. for $C_{10}H_{16}O_2$: 168.1150). Anal. Calcd. for $C_{10}H_{16}O_2$: C 71.38, H 9.59; Found: 71.40, H 9.68.

B. From dl-10-camphorsulfonic acid sodium salt

To the fused potassium hydroxide (115 g, 2.05 mol) in a porcelain casserole, was added slowly with stirring dl-10-camphorsulfonic acid sodium salt (100 g, 0.39 mol). The heat source was carefully controlled to prevent the charring of the molten mass. After the addition (ca. 20 min), the molten mass was allowed to cool to room temperature and then dissolved in water (500 mL). The resulting solution was washed with ether and the aqueous fraction acidified with ice-cold 6 N hydrochloric acid solution then extracted with dichloromethane. The extracts were combined, dried, filtered and concentrated. The crude residue was distilled as before to give acid **34** (58 g, 78% yield). The spectral data were identical in all respects to those obtained previously (vide supra).

Methyl campholenate (**40**)

To a solution of campholenic acid **34** (45.0 g, 0.28 mol) in acetone (250 mL), anhydrous potassium carbonate (89.7 g, 0.65 mol) was added. After stirring under an argon atmosphere for 1 h, methyl iodide (33.3 mL, 0.53 mmol) was added and the mixture stirred for an additional 18 h. The reaction mixture was then filtered. The solid material was dissolved in water and extracted with dichloromethane. The dichloromethane extract and acetone filtrate were combined. After most of the solvent had been evaporated, the mixture was taken up in dichloromethane (200 mL) and washed with ice-cold 2 N hydrochloric acid solution, water and saturated aqueous sodium chloride solution. The organic fraction was dried, filtered and concentrated. The residue was distilled to afford the pure ester **40** (48 g, 98% yield): 83-86°C/0.5 torr; ir 1748 cm^{-1} (ester); nmr δ 5.22 (br, s, 1H, $=\overset{|}{C}H$), 3.68 (s, 3H, $-COOCH_3$), 1.62 (br, s, 3H, $=\overset{|}{C}CH_3$), 0.98 (s, 3H, $-CH_3$) and 0.78 (s, 3H, $-CH_3$); ms M^+ 182.1305 (calcd. for $C_{11}H_{18}O_2$: 182.1307). Anal. Calcd. for $C_{11}H_{18}O_2$: C 72.45, H 9.95; Found: C 72.12, H 9.82.

4-Carbomethoxymethyl-3,3-dimethyl-2-methylidenecyclopentanol (**41**)

A solution of the ester **40** (5.0 g, 27.5 mmol) and methylene blue (200 mg) in methanol (250 mL) was irradiated with two 200 W tungsten light bulbs for 72 h. During this period a moderate stream of oxygen was bubbled through the solution. The solution was cooled at 0°C and sodium borohydride (0.39 g, 10.3 mmol) was added. After stirring for 1 h, it was poured into ice-cold 2 N aqueous hydrochloric acid solution (300 mL) and extracted with chloroform (3 x 100 mL). The combined chloroform extract was dried, filtered and concentrated. The residue was chromatographed on silica gel, eluting with 15% ethyl acetate in petroleum ether to give a 7:3 mixture of two epimeric allylic alcohols **41** (3.6 g, 66% yield): ir 3440 (alcohol), 3106, 1650 (olefin) and 1746 cm^{-1} (ester); nmr δ 5.16, 5.10, (br, s, total 1H, -C$\underline{H}$H) and 5.02, 4.92 (br, s, total 1H, =CH$\underline{H}$); 4.40 (m, 1H, -C$\underline{H}$OH) 3.66 (s, 3H, $-CO_2CH_3$), 1.12, 1.02, 0.92 and 0.82 (s, total 6H, 2 x $-CH_3$); ms M^+ 198.1256 (calcd. for $C_{11}H_{18}O_3$: 198.1256).

4-Carbomethoxymethyl-3,3-dimethyl-2-methylidenecyclopentanone (42)

A solution of dimethyl sulfoxide (14.1 mL, 0.20 mol) in dichloromethane (25 mL) was added dropwise to a solution of oxalyl chloride (6.9 mL, 79 mmol) at -78°C under an argon atmosphere. The mixture was stirred for 15 min after which a solution of hydroxy esters **41** (11.2 g, 56 mmol) in dichloromethane (25 mL) was added dropwise. The mixture was stirred for 1 h at -78°C. Triethylamine (25 mL) in dichloromethane (25 mL) was added dropwise and the reaction was allowed to warm up to room temperature overnight. It was poured into ice-cold water and the organic fraction separated, washed with water, dried, filtered and concentrated. The residue was chromatographed on silica gel. Elution with 5% ethyl acetate in petroleum ether afforded the pure enone 42 (9.4 g, 85%): ir 1748 (ester), 1729 (α,β-unsaturated ketone), 1634 and 1605 cm^{-1} (C=C); nmr δ 5.98 (br, s, 1H, =CHH); 5.20 (br, s, 1H, =CHH), 3.68 (s, 3H, $-CO_2CH_3$), 2.54 (dd, 1H, J = 18, J' = 7 Hz, -COCHH-), 2.06 (dd, 1H, J = 18, J' = 11 Hz, -COCHH-), 1.22 (s, 3H, $-CH_3$) and 1.00 (s, 3H, $-CH_3$); ms M^+ 196.1099 (calcd. for $C_{11}H_{16}O_3$: 196.1099. Anal. Calcd. for $C_{11}H_{16}O_3$: C 67.30, H 8.22; Found: C 67.20, H 8.12.

Enone ester 42 from modified photo-oxygenation reaction

The reactor was charged with a solution of ester 40 (5.0 g, 27.5 mmol) in dichloromethane (200 mL), acetic anhydride (2.74 mL, 29 mmol), pyridine (1.11 mL, 13.7 mmol), 4-dimethylaminopyridine (60 mg, 0.5 mmol) and 5,10,15,20-tetraphenyl-21H,23H-porphine (15 mg). The reaction was irradiated with two 200 W tungsten light bulbs for 24 h. During this period a moderate stream of oxygen was bubbled through the solution. The reaction mixture was then let to stand without radiation for 2 h. The reaction mixture was then diluted with ether and washed with saturated aqueous sodium bicarbonate solution, 1 N hydrochloric acid solution, saturated cupric sulfate solution and saturated sodium chloride solution. The organic extract was dried, filtered and concentrated. Flash chromatography of the residue on silica gel, eluting with 10% ethyl acetate in petroleum ether gave enone **42** (3.87 g, 72% yield). The spectral data were consistent with those obtained previously (vide supra).

Reaction of enone ester **42** with acryloyl chloride

Enone ester **42** (300 mg, 1.53 mmol), sodium acetate (310 mg, 3.73 mmol) and acryloyl chloride (4 mL) were stirred at room temperature for 1 h then refluxed for an additional 24 h under an argon atmosphere. The reaction was cooled to room temperature. Aqueous 1 N sodium hydroxide solution was added then extracted with dichloromethane and ether. The organic extracts were then washed with concentrated sodium chloride solution, dried, filtered and evaporated. Flash chromatography of the residue on silica gel, eluting with 15% ethyl acetate in petroleum ether gave the required enol ester **45** (64 mg, 18%): ir 1737 (ester), 1630 and 1600 cm^{-1} (C=C); nmr δ 6.54 (dd, 1H, J = 18, J' = 2 Hz, vinyl proton H_a), 6.23 (dd, 1 H, J = 18, J' = 11 Hz, vinyl proton H_b), 5.97 (dd, 1H, J = 11 Hz, J' = 2 Hz, vinyl proton H_c), 4.73 (s, 1 H, H_d), 4.94 (s, 1H, H_e), 5.92 (br, s, vinyl proton H_f), 3.73 (s, 3H, $-COOCH_3$), 1.22 (s, 3H, $-CH_3$) and 1.04 (s, 3H, $-CH_3$); ms M^+ 250.1202 (calcd. for $C_{14}H_{18}O_4$: 250.1205). Further elution with the same solvent system gave chloro compound **46** (38 mg, 9% yield): ir 1769 (enol ester), 1738 (ester), 1628 and 1602 cm^{-1} (C=C); nmr δ 5.92 (s, 1H, $=C\underline{H}H$), 4.94 (s, 1H, $=CH\underline{H}$), 4.73 (br, s, 1H, =CH-), 3.84 (t, 2H, J = 7 Hz, $-CH_2Cl$), 3.70 (s, 3H, $-COOCH_3$), 2.98 (t, 2H, J = 7 Hz, $-C\underline{H_2}CH_2Cl$), 1.20 (s, 3H, $-CH_3$) and 1.02 (s, 3H, $-CH_3$); ms M^+ 286.0972 and 288.0967 (calcd. for $C_{14}H_{19}O_4Cl$: 286.0972). The aqueous layer was acidified with aqueous 1 N hydrochloric acid then extracted with dichloromethane. The extracts were combined, dried and concentrated to give a crude acid (236 mg, 57% yield). A mixture of the acid and potassium carbonate (280 mg, 2.03 mmol) in acetone (10 mL) was stirred at room temperature under argon atmosphere for 40 min. Methyl iodide (0.27 mL, 4.4 mmol) was added and the mixture stirred for an additional 6 h. The reaction mixture was acidified with aqueous 1 N hydrochloric acid solution then extracted with dichloromethane to give ester **48** (243 mg, 98% yield) after concentration and purification by flash chromatography (15% ethyl acetate in petroleum ether): ir 1737 (ester) and 1640 cm^{-1} (C=C); nmr δ 3.70 (s, 3H, $-COOCH_3$), 3.65 (s, 3H, $-COOCH_3$), 3.74 (dd, 1H, J = 8, J' = 5 Hz, $-C\underline{H}HO-$), 3.72 (dd, 1H, J = 8, J = 3 Hz, $-CH\underline{H}O-$), 1.90 (d, 2H, J = 7 Hz, $-CH_2-$), 0.92 (s, 3H, $-CH_3$) and 0.75 (s, 3H, $-CH_3$); ^{13}C nmr δ 173.93, 171.71, 121.29, 116.54, 58.87, 51.69, 51.41, 50.13, 46.53, 41.65, 34.72, 32.2850, 17.5608, 16.0795 and 9.4641; ms M^+ 282.1469 (calcd. for $C_{15}H_{22}O_5$: 282.1477).

Reaction of **42** and acryloyl chloride in refluxing toluene

A mixture of enone **42** (386 mg, 1.98 mmol), potassium carbonate (200 mg, 1.45 mmol) and acryloyl chloride (3 mL) in toluene (6 mL) was refluxed under an argon atmosphere for 72 h. After this period an additional amount of acryloyl chloride (1 mL) in toluene was added and the mixture continued refluxing for another 6 h. The reaction mixture was cooled and washed with ice-cold 1 N hydrochloric acid solution and saturated sodium chloride solution. The organic extract was dried, filtered and concentrated. Flash chromatography of the residue on silica gel (15% ethyl acetate in petroleum ether) gave the required enol ester **45** (238 mg, 53% yield), chloro compound **46** (35 mg, 6% yield) and another mixture (62 mg) which was difficult to purify.

Claissen type rearrangement of enol ester **45**

Enol ester **45** (124 mg, 0.5 mmol) in xylene (3 mL) was refluxed under an argon atmosphere for 1 h. After this period, 1-pentanol (1 mL, 92 mmol) was added and refluxing was continued for an additional 48 h. The solution was cooled to room temperature and acidified with ice cold 1 N hydrochloric acid solution then extracted with dichloromethane. The organic extracts were combined, dried, filtered and concentrated. The residue was chromatographed on silica gel eluting with 15% ethyl acetate in petroleum ether to give diester **52** (56 mg, 33% yield): ir 1738 cm^{-1} (ester) and 1642 cm^{-1} (C=C); nmr δ 6.40 (s, 1H, =C$\underline{H}$H), 5.22 (s, 1H, =CH$\underline{H}$), 3.97 (t, 2H, $\underline{J}$ = 7 Hz, $-OCH_2-$), 3.70 (s, 3H, $-COOCH_3$) 1.20 (s, 3H, $-CH_3$), 1.04 (s, 3H, $-CH_3$) and 0.92 (t, 3H, J = 7 Hz, $-CH_2CH_3$); ms M^+ 338.2093 (calcd. for $C_{19}H_{30}O_5$: 338.2093). Further elution with the same solvent system gave unreacted enol ester **45** (51 mg, 41% recovery).

5-Carbomethoxymethyl-4,4-dimethyl-7-oxo-1-oxaspiro[2.4]-heptane (57)

A solution of enone **42** (3.18 g, 16 mmol) in methanol (50 mL) was stirred at 0°C for 15 min. A solution of hydrogen peroxide (30% aqueous solution, 5.5 mL, 49 mmol) and lithium hydroxide monohydrate (105 mg, 2.4 mmol) was added slowly. The reaction mixture turned yellow then colourless. It was stirred at 0°C for 20 min then at room temperature under an atmosphere of argon for 3 h. Ice cold water and diluted hydrochloric acid solution were added and then the solution extracted with methylene chloride. The organic solution was dried, filtered and concentrated to give a 1:1 mixture of epimeric epoxides **57**

(2.97 g, 86% yield). Flash chromatography of the mixture on silica gel eluting with 25% ethyl acetate in petroleum ether gave one of the epoxides: ir 1742 (ketone) and 1738 cm^{-1} (ester); nmr δ 3.76 (s, 3H, $-COOCH_3$), 3.15 (d, 1H, J = 6 Hz, -OCHH-), 2.85 (d, 1H, J = 6 Hz, -OCHH-), 1.04 (s, 3H, $-CH_3$) and 0.98 (s, 3H, $-CH_3$); ms M^+ 212.1043 (calcd. for $C_{11}H_{16}O_4$: 212.1049). Anal. Calcd. for $C_{11}H_{16}O_4$: C 62.23, H 7.60; Found: C 62.20, H 7.72. Further elution with the same solvent system gave the other epoxide **57**: ir 1742 (ketone) and 1736 cm^{-1} (ester); nmr δ 3.72 (s, 3H, $-COOCH_3$), 3.00 (d, 1H, J = 6 Hz, -OCHH-), 2.96 (d, 1H, J = 6 Hz, -OCHH-), 1.00 (s, 3H, $-CH_3$) and 0.94 (s, 3H, $-CH_3$); ms M^+ 212.1046 (calcd. for $C_{11}H_{16}O_4$: 212.1049).

4-Carbomethoxymethyl-3,3-dimethylcyclopentanone (**53**) and 5-carbomethoxymethyl-6,6-dimethyl-3-methoxy-2-cyclohexenone (**59**)

To a hot solution of epoxides **57** (8.17 g, 38.5 mmol) in methanol (25 mL) was added slowly a solution of sodium hydroxide (5.30 g, 133 mmol) in methanol (35 mL). The mixture was refluxed for 2 h. Water (5 mL) was added and refluxing was continued for an additional 72 h. The solution was allowed to cool to room temperature, acidified with 6 N hydrochloric acid solution and extracted with methylene chloride. The organic extracts were dried, filtered and concentrated giving a crude acid (5.84 g): ir 3500-2500 (acid), 1737 (ketone), and 1709 cm^{-1} (acid). To a solution of this acid in acetone (50 mL), anhydrous potassium carbonate (16.1 g, 116.5 mmol) was added. The mixture was stirred at room temperature under an argon atmosphere for 1 h and methyl iodide (6.4 mL, 103 mmol) added. After a gentle reflux overnight, the reaction mixture was poured into ice-cold water and extracted with methylene chloride. The organic solution was dried, filtered and concentrated. Flash chromatography of the residue on silica gel, eluting with 15% ethyl acetate in petroleum ether gave ester **53** (3.82 g, 54% yield): ir 1740 cm^{-1} (ketone and ester); ^{1}H nmr, δ 3.70 (s, 3H, $-COOCH_3$), 2.14 (s, 2H, $-COCH_2-\overset{|}{C}(CH_3)_2$), 1.18 (s, 3H, $-CH_3$) and 0.92 (s, 3H, $-CH_3$); ms M$^+$ 184.1097 (calcd. for $C_{10}H_{16}O_3$: 184.1099). Anal. Calcd. for $C_{10}H_{16}O_3$: C 65.19, H 8.75; Found: C 65.24, H 8.58. Further elution with the same solvent system gave compound 59 (1.72 g, 20% yield): ir 1730 (ester), 1710 (ketone) and 1620 cm^{-1} (C=C); nmr δ 7.15 (s, 1H, $=\overset{|}{C}H$), 3.86 (s, 3H, $-COOCH_3$), 3.72 (s, 3H, $-OCH_3$), 2.52 (m, 2H, $-CH_2-$), 2.30 (m, 2H, $-CH_2-$), 2.10 (dd, 1H, J = 11, J' = 7 Hz, $=\overset{|}{C}C\underline{H}H-$), 1.32 (s, 3H, $-CH_3$) and 1.04 (s, 3H, $-CH_3$); ms M$^+$ 226.1204 (calcd. for $C_{12}H_{18}O_4$: 226.1205). ^{13}C nmr: δ 203.33, 172.13, 154.70, 123.39, 61.15, 50.52, 42.02, 40.68, 40.57, 33.23, 24.75 and 20.14.

When the reaction was carried out at 0°C, keto ester **59** was isolated as the only product.

2-Hydroxymethyl-3,3-dimethyl-4-carbomethoxymethylcyclopentanone (**62**) and keto ester **63**

To a solution of epoxides **57** (145 mg, 0.68 mmol) in acetic acid (5 mL) was added zinc metal (133 mg, 2.04 mmol). The reaction was refluxed for 2 h under an argon atmosphere. The mixture was cooled to room temperature then filtered. The filtrate was diluted with ether, washed with aqueous sodium bicarbonate solution, aqueous 1 N hydrochloric acid and water. The organic extract was dried, filtered and concentrated. Flash chromatography of the residue on silica gel, eluting with 20% ethyl acetate in petroleum ether gave keto ester **63** (44 mg, 33% yield): ir (neat) 1739 cm^{-1} (ketone and ester); nmr, δ 3.70 (s, 3H, $-COOCH_3$), 2.04 (q, 1H, J = 8.5 Hz, $-\overset{|}{C}HCO-$), 1.12 (s, 3H, $-CH_3$), 0.96 (d, 3H, J = 8.5, CH_3-) and 0.85 (s, 3H, $-CH_3$); ms M^+ 198.1262 (calcd. for $C_{11}H_{18}O_3$: 198.1265). Further elution using the same solvent system afforded hydroxy ester **62** (20 mg, 14% yield): ir (neat) 3540 (alcohol), 1740 (ketone and ester); nmr δ 3.70 (m, 5H, $-C\underline{H_2}OH$, $-COOCH_3$), 1.06 (s, 3H, $-CH_3$) and 0.84 (s, 3H,

$-CH_3$); ms M^+ 214.1206 (calcd. for $C_{11}H_{18}O_4$: 214.1205). Unreacted epoxides **57** were recovered (74 mg, 51% recovery).

Hydroxy ester 62

To a solution of epoxides **57** (452 mg, 213 mmol) in benzene (10 mL) was added acetic acid (1 mL) and zinc metal (418 mg, 6.40 mmol). The reaction was refluxed for 2 h under an atmosphere of argon. The extraction and purification were performed as before. Hydroxy ester **62** (172 mg, 38% yield) and epoxides **57** (207 mg, 49% recovery) were obtained. All the spectra data were identical to the ones obtained previously.

Treatment of epoxides 57 with sodium hydride

To a suspension of sodium hydride (80% dispersion in oil; 202 mg, 6.73 mmol), freed from mineral oil by washing with petroleum ether (3 x 5 mL), in benzene (10 mL), a solution of epoxides **57** (1.1 g, 5.2 mmol) in benzene (5 mL) was added. After stirring for 1 h under an argon atmosphere at room temperature, the reaction mixture was heated at reflux for an additional 14 h. Ice-cold water and diluted hydrochloric acid solution were added and the mixture extracted with methylene chloride. The combined organic extracts were washed with saturated aqueous sodium chloride solution, dried, filtered and concentrated.

Flash chromatography of the residue on silica gel, eluting with 15% ethyl acetate in petroleum ether gave keto ester **53** (167 mg, 18% yield) and unreacted epoxides **57** (810 mg, 74% recovery). The spectral data were identical to those obtained previously (*vide supra*).

2-Carboethoxyethyl-3-carbomethoxymethyl-4,4-dimethylcyclopentanone (65)

To sodium hydride (36.4 mg, 1.21 mmol) in 1,2-dimethoxyethane (5 mL) was added keto ester **53** (216 mg, 1.17 mmol). The mixture was stirred at room temperature for 1 h under an argon atmosphere. Ethyl acrylate (0.15 mL, 1.38 mmol) was then added and stirring continued for additional 24 h. The mixture was taken up in dichloromethane (5 mL) and washed with dilute hydrochloric acid, water and saturated aqueous sodium chloride solution. The organic layer was dried, filtered and concentrated. Flash chromatography of the residue on silica gel, eluting with 15% ethyl acetate in petroleum ether gave diester **65** (276 mg, 83% yield); ir 1739 cm^{-1} (esters and ketone); nmr, δ 4.12 (q, 2H, J = 8 Hz, $-COOC\underline{H_2}CH_3$), 3.72 (s, 3H, $-COOCH_3$), 2.18 (s, 2H, $-COCH_2\overset{|}{\underset{|}{C}}-$), 1.32 (t, 3H, J = 8 Hz, $-COOCH_2C\underline{H_3}$), 1.08 (s, 3H, $-CH_3$) and 0.94 (s, 1H, $-CH_3$); ms M^+ 284.1624 (calcd. for $C_{15}H_{24}O_5$: 284.1624).

2,5-Dicarboethoxyethyl-3-carbomethoxymethyl-4,4-dimethylcyclopentanone (71)

To a suspension of sodium hydride (111 mg, 3.7 mmol) in 1,2-dimethoxyethane (10 mL) was added keto ester **53** (566 mg, 3.1 mmol). The mixture was stirred at room temperature for 20 min under an argon atmosphere. After this period, the temperature was raised to 60°C and ethyl acrylate (0.44 mL, 4.1 mmol) added dropwise. The mixture was stirred for additional 3 h, cooled to room temperature, taken up in dichloromethane and washed with 1 N hydrochloric acid solution and saturated aqueous sodium chloride solution. The organic layer was dried, filtered and concentrated. Flash chromatography of the residue on silica gel, eluting with 20% ethyl acetate in petroleum ether gave triester 71 (898 mg, 76% yield); ir (neat) 1740 cm^{-1} (ketone and esters); nmr δ 4.12 (q, 4H, J = 8 Hz, 2 x $-COO-C\underline{H_2}CH_3$), 3.65 (s, 3H, $-COOCH_3$), 2.27 (t, 1H, J = 6.5 Hz, $-CO\overset{|}{C}H-$) and 1.22-0.98 (set of seven peaks, 12H, 2 x $-CH_3$, 2 x $-OCH_2\underline{CH_3}$); ms M^+ 384.2148 (calcd. for $C_{20}H_{32}O_7$: 384.2148).

2-Carboethoxyethyl-3-carbomethoxymethyl-1,1-ethylenedithio-4,4-dimethylcyclopentane (69)

At 0°C, to a solution of diester **65** (227 mg, 1.23 mmol) in dichloromethane (5 mL) were sequentially added

1,2-ethanedithiol (0.2 mL, 2.61 mmol) and boron trifluoride etherate (0.1 mL, 0.8 mmol). After stirring under an argon atmosphere for 6 h, ice-cold 1 N aqueous potassium hydroxide solution was added and the resulting mixture extracted with methylene chloride. The organic extracts were washed with water, dried, filtered and concentrated. Flash chromatography of the residue on silica gel, eluting with 10% ethyl acetate in petroleum ether gave thioketal **69** (235 mg, 82% yield): ir (neat) 1737 cm^{-1} (esters); nmr δ 4.14 (q, 2H, J = 7.5 Hz, $-O-C\underline{H_2}CH_3$), 3.70 (s, 3H, $-COOCH_3$), 3.33 (m, 4H, $-SCH_2CH_2S-$), 2.28 (s, 2H, $-CH_2\overset{|}{\underset{|}{C}}-$), 1.28 (t, 3H, J = 7.5 Hz, $-OCH_2C\underline{H_3}$), 1.04 (s, 3H, $-CH_3$) and 0.94 (s, 3H, $-CH_3$); ms M^+ 360.1432 (calcd. for $C_{17}H_{28}S_2O_4$: 360.1429).

4-Carboethoxy-7,7-ethylenedithio-9,9-dimethylbicyclo-[4.3.0]nonan-3-one (**70**)

To a suspension of sodium hydride (80% dispersion in oil, 46 mg, 1.53 mmol) in toluene (10 mL), a solution of thioester **69** (429 mg, 1.19 mmol) in toluene (1 mL) and two drops of methanol were added. The reaction mixture was then refluxed for 5 h under an argon atmosphere. The reaction mixture was allowed to cool to room temperature, acidified with dilute aqueous hydrochloric acid solution and extracted with dichloromethane. The organic extracts were dried, filtered and concentrated. Flash chromatography of the residue on silica gel, eluting with 5% ethyl acetate in petroleum ether afforded thiolester **70** (266 mg, 68% yield); ir 1735 (ketone and ester), 1656 and 1610 cm^{-1} (β-hydroxy α,β-unsaturated ester); nmr δ 4.10 (q, 2H, J = 7 Hz, $-O-C\underline{H_2}CH_3$), 3.27 (m, 4H, $-SCH_2CH_2S-$), 2.26 (s, 2H, $-CH_2\overset{|}{\underset{|}{C}}-$), 1.27 (t, 3H, J = 7 Hz, $-OCH_2C\underline{H_3}$), 1.08 (s, 3H, $-CH_3$) and 0.92 (s, 3H, $-CH_3$); ms M$^+$ 328.1169 (calcd. for $C_{16}H_{24}O_3S_2$: 328.1167).

4-Carboethoxy-9,9-dimethylbicyclo[4.3.0]nona-3,7-dione (**66**)

A solution of the dithiane **70** (219 mg, 0.68 mmol) in aqueous 80% acetonitrile (2 mL) was added at 25°C to a stirring solution of mercuric chloride (399 mg, 1.47 mmol), calcium carbonate (147 mg, 1.47 mmol) in aqueous 80% acetonitrile (5 mL). The mixture was heated at reflux under an argon atmosphere for 4 h. The solution was then cooled and filtered. The precipitate was washed thoroughly with 1:1 hexane/dichloromethane. The organic phase of the filtrate was washed with 5 M aqueous ammonium acetate, water, saturated sodium chloride solution then dried, filtered and concentrated. The residue was purified by flash chromatography over silica gel, eluting with 10% ethyl acetate in petroleum ether to afford diketo ester **66**: (75.7 mg, 45% yield); ir 1738 (carbonyl), 1656 and 1601 cm^{-1} (enolized β-keto ester); nmr δ 4.08 (q, 2H, J = 7.5 Hz, $-O-C\underline{H_2}CH_3$), 2.18 (s, 2H, $-CH_2\overset{|}{\underset{|}{C}}-$), 1.28 (t, 3H, J = 7.5 Hz, $-OCH_2\underline{CH_3}$), 1.22 (s, 3H, $-CH_3$) and 1.00 (s, 3H, $-CH_3$); ms M^+ 252.1362 (calcd. for $C_{14}H_{20}O_4$: 252.1361).

2-Carboethoxyethyl-3-carbomethoxymethyl-4,4-dimethyl pentanone (**65**) Using LDA as a base

A solution of 1.35 M methyllithium (1.46 mL, 1.97 mmol) in hexane was added at -78°C to a solution of diisopropylamine (0.279 mL, 1.99 mmol) in dry tetrahydrofuran (10 mL) under an argon atmosphere. After stirring for 40 min, a solution of keto ester **53** (303 mg, 1.65 mmol) in 2 mL of tetrahydrofuran was added dropwise and stirring was continued for an additional 1 h. Ethyl acrylate (0.214 mL, 1.98 mmol) was added and the reaction mixture allowed to warm up to room temperature over 4 h period. The mixture was taken up in dichloromethane then washed with aqueous 1 N hydrochloric acid solution and aqueous saturated sodium chloride solution. The organic layer was dried, filtered and concentrated. On purification by flash chromatography (silica gel, 15% ethyl acetate in petroleum ether), diester **65** (401 mg, 86% yield) was produced. The ir, nmr and mass spectra were identical to those obtained previously.

2-Carbomethoxyethyl-3-carbomethoxymethyl-4,4-dimethylcyclopentanone (**72**) and 4-carbomethoxy-9,9-dimethylbicyclo[4.3.0]nona-3,7-dione (**73**)

A solution of 1.20 M methyllithium (2.34 mL, 2.81 mmol) in hexane was added at -78°C to a solution of diisopropylamine (0.393 mL, 2.80 mmol) in 10 mL of dry tetrahydrofuran under an argon atmosphere. After stirring for 40 min, a solution of keto ester **53** (430 mg, 2.34 mmol) in 2 mL of tetrahydrofuran was added dropwise followed by hexamethylphosphoramide (0.488 mL, 2.80 mmol) and stirring was continued for 1 h. Methyl acrylate (0.231 mL, 2.56 mmol) was added and the reaction mixture let to warm up to 0°C over a 5 h period. The reaction mixture was taken up in dichloromethane, washed with aqueous 1 N hydrochloric acid solution and saturated aqueous sodium chloride solution. The organic layer was dried, filtered and concentrated. Purification by flash chromatography on silica gel, eluting with 10% ethyl acetate in petroleum ether gave diketo ester **73** (192 mg, 35% yield). ir 1738 cm^{-1} (carbonyl), 1659 and 1604 cm^{-1} (β-hydroxy α,β-unsaturated ester); nmr δ 13.56 (s, 1H, $=\overset{|}{C}-OH$), 3.77 (s, 3H, $-COOCH_3$), 2.12 (s, 2H, $-COCH_2\overset{|}{\underset{|}{C}}-$), 1.20 (s, 3H, $-CH_3$) and 1.02 (s, 3H, $-CH_3$); ^{13}C nmr: δ 215.9022, 172.7809, 172.0691, 96.6322, 53.7887, 51.3241, 47.2978, 46.9170, 35.4030, 29.7600, 27.7923, 22.2262, 21,7813; ms M^+ 238.1205 (calcd. for $C_{13}H_{18}O_4$: 238.12038). *Anal*. Calcd. for $C_{13}H_{18}O_4$: C 65.51, H 7.56; Found: C 65.29, H 7.42. Further elution using 10% ethyl acetate in petroleum ether gave keto diester **72** (273 mg, 43%): ir 1739 cm^{-1} (ketone and ester); nmr δ 3.75, 3.72, 3.70 and 3.68 (s, total 6H, 2 x $-COOCH_3$), 2.18 (s, 2H, $-COCH_2\overset{|}{\underset{|}{C}}-$), 1.14, 1.13, 0.95 and 0.94 (s, total 6H, 2 x $-CH_3$); ms M^+ 270.1467 (calcd. for $C_{14}H_{22}O_5$: 270.1467).

Compounds 72, 73 and 4-carbomethoxyethyl-4-carbomethoxy-9,9-dimethylbicyclo[4.3.0]nona-3,7-dione (74)

A solution of 1.35 M methyllithium (7.40 mL, 9.98 mmol) in hexane was added at -78°C to a solution of diisopropylamine (1.40 mL, 9.98 mmol) in 25 mL of dry tetrahydrofuran under an argon atmosphere. After stirring for 40 min, a solution of keto ester **53** (1.67 g, 9.08 mmol) in tetrahydrofuran (5 mL) was added dropwise followed by hexamethylphosphoramide (1.74 mL, 9.98 mmol) then warmed up to -40°C. Methyl acrylate (0.90 mL, 9.98 mmol) was added and the reaction mixture left stirring for 2 h. After this period, the mixture was again warmed up to 0°C over a 4 h period. The mixture was taken up in dichloromethane, washed thoroughly with ice-cold aqueous 1 N hydrochloric acid and saturated sodium chloride solution. The organic layer was dried, filtered and concentrated. Flash chromatography of the residue on silica gel, eluting with 10% ethyl acetate in petroleum ether gave: diketo ester **73** (1.03 g, 48% yield) and keto diester **72** (569 mg, 23% yield). The spectra data were identical to those obtained previously (vide supra). Further elution using 15% ethyl acetate in petroleum ether gave diketo ester **74** (247 mg, 18% yield): ir 1739 (esters and five membered ketone) and 1713 cm^{-1} (cyclohexanone): nmr δ 3.75 (s, 1H, $-COOCH_3$), 3.65 (s, 3H, $-COOCH_3$), 2.30 (s, 2H, $-COCH_2\overset{|}{\underset{|}{C}}-$), 1.18 (s, 3H, $-CH_3$) and 0.92 (s, 3H, $-CH_3$); ms M^+ 324.1573 (calcd. for $C_{17}H_{24}O_6$: 324.1572).

Keto diester **72** from methyl β-bromopropionate

A solution of 1.18 M methyllithium (6.01 mL, 7.09 mmol) in hexane was added at -78°C to a solution of diisopropylamine (0.99 mL, 7.09 mmol) in 20 mL of dry tetrahydrofuran under an argon atmosphere. After stirring for 1 h, a solution of keto ester **53** (870 mg, 4.73 mmol) in tetrahydrofuran (3 mL) was added dropwise followed by hexamethylphosphoramide (1.23 mL, 7.09 mmol) and the mixture was stirred for 1 h. Methyl β-bromopropionate (0.671 mL, 6.15 mmol) was added and the mixture warmed up to room temperature over a period of 10 h. The mixture was taken up in dichloromethane, washed with aqueous 2 N hydrochloric acid solution and saturated solution of sodium chloride. The organic layer was dried, filtered and concentrated. Purification by flash chromatography over silica gel, eluting with 10% ethyl acetate in petroleum ether gave diketo ester **73** (232 mg, 14% yield), keto ester **53** (342 mg, 39% recovery) and keto diester **72** (523 mg, 42% yield). All the spectral data were identical to those recorded previously (vide supra).

4-Carbomethoxy-4-formylethyl-9,9-dimethylbicyclo[4.3.0]-nona-3,7-dione (77)

To a solution of diketo ester **73** (37 mg, 0.16 mmol) in 1,2-dimethoxyethane (2 mL) was added 1,4-diazabicyclo-[2.2.2]octane (20.3 mg, 0.18 mL). After stirring for 20 min under an argon atmosphere at room temperature, acrolein (0.0143 mL, 0.21 mmol) was added. Stirring was continued for 4 h. The reaction mixture was taken up in ether (5 mL) and washed with aqueous 1 N hydrochloric acid solution. The organic layer was dried, filtered and concentrated. Flash chromatography of the residue on silica gel eluting with 15% ethyl acetate in petroleum ether afforded adduct **77** (41 mg, 90% yield): ir 2860, 2720 (aldehyde), 1740 (ester, cyclopentanone) and 1713 cm^{-1} (aldehyde and cyclohexanone); nmr δ 9.66 (br, s, 1H, -CHO), 3.72 (s, 3H, -COOCH$_3$), 1.08 (s, 3H, -CH$_3$) and 1.02

(s, 3H, $-CH_3$); ms M^+ 294.1466 (calcd. for $C_{16}H_{22}O_5$: 294.1467).

4-Carbomethoxy-4,9,9-trimethylbicyclo[4.3.0]nona-3,7-dione (**78** and **79**)

Potassium hydride (35% dispersion in mineral oil, 272 mg, 2.37 mmol) was washed (3 x 3 mL) under an argon atmosphere with petroleum ether and then tetrahydrofuran (10 mL) added. Diketo ester **73** (502 mg, 2.11 mmol) in tetrahydrofuran (2 mL) was added via a glass syringe and the resulting mixture stirred for 25 min at 0°C. The enolate was treated with iodomethane (0.146 mL, 2.35 mmol) then stirred for 8 h at room temperature. The reaction mixture was diluted with water then extracted with ether. The organic extracts were combined, washed with saturated sodium chloride solution, dried, filtered and concentrated. Flash chromatography of the residue on silica gel eluting with 15% ethyl acetate in petroleum ether gave a mixture of diastereomers **78** and **79** (ca. 2:1 ratio by nmr analysis; 492 mg, 93% yield): ir 1741 (cyclopentanone and ester) and 1710 cm^{-1} (cyclohexanone); ms M^+ 252.1361 (calcd. for $C_{14}H_{20}O_4$: 252.1363). Anal. Calcd. for $C_{14}H_{20}O_4$: C 66.67, H 7.94; Found: 66.53, H 7.84. Diketo ester **78** (m.p. 75-76°C) was separated from **79** by recrystallization from ethyl acetate/petroleum ether. The following nmr data was obtained for **78**: δ 3.74 (s, 3H, $-COOCH_3$), 2.54 (dd, J = 15, J' = 5 Hz, $1H_b$), 2.48 (dd, J = 15, J' = 13 Hz, $1H_a$), 2.35 (dd, J = 19, J' = 2 Hz, $1H_g$), 2.26 (t, J = 13 Hz, $1H_e$), 2.46 (ddd, J = J' = 13, J" = 5 Hz, $1H_d$), 1.90 (ddd, J = J' = 13, J = 5 Hz, $1H_c$), 1.43 (s, 3H, $-CH_3$), 1.17 (s, 3H, $-CH_3$), 1.07 (s, 3H, $-CH_3$).

Diketo esters **78** and **79** by use of potassium carbonate as a base

Potassium carbonate (582 mg, 4.21 mmol) in acetone (10 mL) was stirred for 40 min at room temperature under argon atmosphere. Sequentially keto ester **73** (334 mg, 1.40 mmol) in acetone (2 mL) and iodomethane (0.174 mL, 2.79 mmol) were added and the reaction mixture continued stirring for 24 h. After this period ice-cold dilute hydrochloric acid solution was added and then extracted with dichloromethane. The organic extracts were combined, dried, filtered and concentrated. The residue was chromatographed on silica gel eluting with 15% ethyl acetate in petroleum ether to afford diastereomeric esters **78** and **79** (293 mg, 82% yield). The unreacted **73** was also obtained (43 mg, 15% recovery). All the spectra data were identical to those obtained previously (vide supra).

Conversion of **78** to **79**

To a solution of diketo ester **78** (122 mg, 0.48 mmol) in acetone (4 mL) was added potassium carbonate (134 mg, 0.97 mmol). The mixture was refluxed for 20 h under an atmosphere of argon. Aqueous 1 N hydrochloric acid solution was added and the resulting solution extracted with dichloromethane. The organic extracts were dried, filtered and concentrated. The residue was chromatographed on silica gel. Elution with a solution of 10% ethyl acetate in petroleum ether gave a mixture of epimers **78** and **79** (*ca*: 1.3 ratio by nmr analysis, 113 mg, 93% yield).

4-Carbomethoxy-3-hydroxy-4,9,9-trimethylbicyclo-[4.3.0]nonan-7-one (**84**)

A solution of diketo ester 78 (80.6 mg, 0.320 mmol) and lithium tri-tert-butoxyaluminium hydride (97.5 mg, 383 mmol) in tetrahydrofuran/ether (1:3, 4 mL) was stirred at room temperature under an atmosphere of argon for 12 h. Water was added and the resulting solution extracted with dichloromethane. The extracts were dried, filtered and concentrated. The residue was chromatographed on silica gel eluting with 15% ethyl acetate in petroleum ether to afford hydroxy esters **84** (78.68 mg, 97% yield): ir 3480 (alcohol) and 1740 cm^{-1} (ketone and ester); nmr δ 3.94

(br, t, 1H, $-\overset{|}{C}\underline{H}-OH$), 3.74 (s, 3H, $-COOCH_3$), 2.18 (d, 1H, J = 13 Hz, $-COC\underline{H}H-$), 2.09 (d, 1H, J = 13 Hz, $-COCH\underline{H}-$), 1.14, 1.12, 1.08, 1.06, 1.03, 1.00 (s, total 9H, 3 x $-CH_3$); ms M^+ 254.1522 (calcd. for $C_{14}H_{22}O_4$: 254.1517).

4-Carbomethoxy-7,7-ethylenedithio-4,9,9-trimethylbicyclo-[4.3.0]nonan-3-ol (85)

At 0°C, to a solution of hydroxy esters **84** (78 mg, 0.307 mmol) in dichloromethane (3 mL) was added sequentially, 1,2-ethanedithiol (0.039 mL, 0.465 mmol) and boron trifluoride etherate (0.045 mL, 0.395 mmol). The resulting mixture was stirred at room temperature overnight under an argon atmosphere. Ice-cold aqueous 1 N potassium hydroxide solution was added and the resulting mixture extracted with methylene chloride. The organic extracts were washed with saturated sodium chloride solution, dried, filtered and concentrated. Flash chromatography of the residue on silica gel, eluting with 15% ethyl acetate in petroleum ether gave thioketal **85** (91.9 mg, 90% yield): ir 3480 (alcohol) and 1731 cm^{-1} (ester); nmr δ 3.97 (br, m, 1H, $-CH_2\overset{|}{C}\underline{H}OH$), 3.70 (s, 3H, $-COOCH_3$), 3.20 (m, 4H, $-SCH_2CH_2S-$), 1.20 (s, 3H, $-CH_3$), 1.02 (s, 3H, $-CH_3$) and 0.95 (s, 3H, $-CH_3$); ms M^+ 330.1322 (calcd. for $C_{16}H_{26}S_2O_3$: 330.1325). Anal. Calcd. C 58.18, H 7.88, S 19.39; Found: C 58.03, H 7.97, S 19.33.

3-Carbomethoxy-4-hydroxy-3,7,7-trimethylbicyclo[4.3.0]-nonane (86)

Freshly prepared Raney nickel (0.5 mL, settled volume) was added to ester **85** (52 mg, 0.158 mmol) in ethanol (98%, 3 mL). The reaction mixture was stirred at room temperature under an argon atmosphere for 2 h. The reaction mixture was carefully filtered and residue washed with ethanol (2 x 1 mL). The filtrate was concentrated, then purified by flash chromatography on silica gel, eluting with 5% ethyl acetate in petroleum ether to afford hydroxy ester **86** (26 mg, 61% yield): ir 3480 (alcohol) and 1731 cm^{-1} (ester); nmr δ 3.97 (br, d, 1H, $-\overset{|}{\mathrm{C}}\underline{\mathrm{H}}\mathrm{OH}$), 3.67 (s, 3H, $-\mathrm{COOCH_3}$), 2.92 (br, s, 1H, -OH), 1.94 (dd, 1H, J = 13.5 Hz, J = 3.5 Hz, $-\mathrm{C}\underline{\mathrm{H}}\mathrm{H}\overset{|}{\mathrm{C}}(\mathrm{CH_3})\mathrm{CO}-$), 1.16 (s, 3H, $-\mathrm{CH_3}$), 0.94 (s, 3H, $-\mathrm{CH_3}$) and 0.77 (s, 3H, $-\mathrm{CH_3}$); ms M^+ 240.1729 (calcd. for $C_{14}H_{24}O_3$: 240.1725).

4-Carbomethoxy-4,9,9-trimethylbicyclo[4.3.0]nonan-3-one (87)

To a solution of hydroxy ester **86** (30 mg, 0.125 mmol) in dichloromethane (3 mL) were added pyridinium chlorochromate (40.4 mg, 0.186 mmol) and sodium acetate (0.46 mg, 35 μmol). The resulting mixture was stirred at room temperature under an argon atmosphere for 3 h. The mixture was filtered and the solid residue washed with ether (3 x 1 mL). The filtrate was concentrated and purified by column chromatography eluting with 5% ethyl acetate in petroleum ether to give keto ester **87** (24 mg, 81% yield): ir 1739 (ester) and 1709 cm^{-1} (cyclohexanone); nmr δ 3.65 (s, 3H, $-COOCH_3$), 1.23 (s, 3H, $-CH_3$), 1.16 (s, 3H, $-CH_3$) and 1.04 (s, 3H, $-CH_3$), ms M^+ 238.1569 (calcd. for $C_{14}H_{22}O_3$: 238.1569).

4-Carbomethoxy-7,7-ethylenedioxy-4,9,9-trimethylbicyclo[4.3.0]nonan-3-ol (**89**)

p-Toluenesulfonic acid monohydrate (31 mg, 0.16 mmol) was dried by refluxing in benzene with azeotropic removal of water. To a solution of dry *p*-toluenesulfonic acid in benzene (2 mL), 2-methyl-2-ethyl-1,3-dioxolane (5 mL) and a solution of hydroxy ester **84** (278 mg, 1.09 mmol) in benzene (2 mL) were added. The mixture was heated at 80-90°C (oil bath temperature) for 4 h. After cooling to 0°C, 10% aqueous sodium bicarbonate soution was added and the mixture extracted with ether. The organic extracts were washed with water and saturated aqueous sodium chloride solution, dried, filtered and concentrated. Flash chromatography of the residue on silica gel, eluting with 10% ethyl acetate in petroleum ether gave ketal **89** (261 mg, 80% yield): ir 3480 (alcohol), 1738 (ester), 1120, 1170 and 1190 cm^{-1} (ketal); nmr δ 3.97 (m, 1H,

-CHOH) 3.87 (m, 4H, $-OCH_2CH_2O-$), 3.70 (s, 3H, $-COOCH_3$), 3.68 (s, 3H, $-COOCH_3$), 1,22, 1.20, 1.02, 1.00, 0.94, 0.93 (s, total 9H, 3 x.$-CH_3$); ms M^+ 298.1781 (calcd. for $C_{16}H_{26}O_5$: 298.1781); Anal. Calcd. C 64.43, H 8.72; Found: C 64.41, H 8.72.

3-Carbomethoxy-9,9-ethylenedioxy-4-methylmercaptothionocarbonyloxy-3,7,7-trimethylbicyclo[4.3.0]nonane (**90**)

At 0°C, to a suspension of sodium hydride (80% dispersion in oil, 119 mg, 3.97 mmol) in freshly distilled 1,2-dimethoxyethane (5 mL) was slowly added under an argon atmosphere a solution of alcohols **89** (236 mg, 0.79 mmol) in 1,2-dimethoxyethane (3 mL). After stirring for 10 min carbon disulfide (0.476 mL, 7.91 mmol) and methyl iodide (0.493 mL, 7.92 mmol) were added. The reaction was stirred at room temperature for 5 h and then cooled to 0°C. Water was added slowly to the reaction mixture and the resulting solution extracted with dichloromethane. Organic layer was washed with water, saturated aqueous sodium chloride then dried, filtered and concentrated. Column chromatography of the residue on silica gel, eluting with 7% ethyl acetate in petroleum ether gave pure **90** (268 mg, 87% yield): ir 1738 (ester), 1220, 1249 (C=S) and 1056 cm^{-1} (C-O-C); nmr δ 3.88 (m, 4H, $-OCH_2CH_2O-$), 3.72 (s, 3H, $-COOCH_3$), 2.48 (s, 3H, $-SCH_3$), 1.24 (s, 3H,

$-CH_3$), 1.00 (s, 3H, $-CH_3$) and 0.94 (s, 3H, $-CH_3$); ms M^+ 388.1378 (calcd. for $C_{18}H_{28}S_2O_5$: 388.1376).

3-Carbomethoxy-9,9-ethylenedioxy-3,7,7-trimethylbicyclo[4.3.0]nonane (91) from xanthate 90

Xanthate **90** (260 mg, 0.61 mmol), azobisisobutylnitrile (50 mg) and tri-*n*-butyltin hydride (0.37 mL, 1.34 mmol) were dissolved in freshly distilled toluene (7 mL). The solution was degassed by bubbling argon through it for 20 min. The resulting solution was refluxed for 3 h at 120°C (oil bath temperature). The reaction mixture was cooled to room temperature and concentrated. The residue on column chromatography over silica gel eluting with 5% ethyl acetate in petroleum ether gave pure **91** as colourless oil (147 mg, 78% yield): ir 1734 cm^{-1} (ester); nmr δ 3.87 (m, 4H, $-OCH_2CH_2O-$), 3.68 (s, 3H, $-COOCH_3$), 1.78 (d, 1H, J = 8 Hz, $-C\underline{H}H\overset{|}{\underset{|}{C}}-$), 1.72 (d, J = 8 Hz, $-CH\underline{H}\overset{|}{\underset{|}{C}}-$), 1.21 (s, 3H, $-CH_3$), 1.02 (s, 3H, $-CH_3$) and 0.94 (s, 3H, $-CH_3$); ms M^+ 282.1831 (calcd. for $C_{16}H_{26}O_4$: 282.1830); *Anal*. Calcd. for $C_{16}H_{26}O_4$: C 68.09, H 9.28; Found: C 68.34, H 9.47.

4-Carbomethoxy-4,9,9-trimethylbicyclo[4.3.0]nonan-7-one (88)

To a solution of *p*-toluenesulfonic acid monohydrate (40.5 mg, 0.21 mmol) in acetone (3 mL) were added ketal **91**

(48.0 mg, 0.17 mmol) and 3 drops of water under an argon atmosphere. The reaction mixture was stirred at room temperature for 2 h. Aqueous 10% sodium bicarbonate solution was added and the resulting mixture extracted with ether. The organic extracts were washed with water and saturated sodium chloride solution, dried, filtered and concentrated. The residue on column chromatography over silica gel, eluting with 5% ethyl acetate in petroleum ether gave pure **88** (38.2 mg, 94%): ir 1741 cm^{-1} (ester); nmr 3.68 (s, 3H, $-COOCH_3$), 2.19 (s, 2H, $-COCH_2\overset{|}{\underset{|}{C}}-$), 1.20 (s, 3H, $-CH_3$), 1.16 (s, 3H, $-CH_3$) and 1.04 (s, 3H, $-CH_3$); ms M^+ 238.1562 (calcd. $C_{14}H_{22}O_3$: 238.1565). *Anal*. Calcd. C 70.56, H 9.24; Found: 70.54, H 9.16.

4-Carbomethoxy-3,3-ethylenedithiol-4,9,9-trimethylbicyclo[4.3.0]nonan-7-one (92)

At 0°C, to a solution of diketo ester **78** (315 mg, 1.25 mmol) in dichloromethane (10 mL) were added sequentially, 1,2-ethanedithiol (0.105 mL, 1.25 mmol), boron trifluoride etherate (0.15 mL, 1.24 mmol). The reaction mixture was stirred at this temperature for 8 h under an argon atmosphere. Ice-cold aqueous 1 N potassium hydroxide solution was added and the resulting mixture extracted with methylene chloride. The organic extracts were washed with saturated sodium chloride solution, dried, filtered and concentrated. Flash chromatography on silica gel, eluting with 10% ethylacetate in petroleum ether gave thioketal **92** (282 mg, 69% yield): ir 1740 cm^{-1} (ester and ketone); nmr δ 3.72 (s, 3H, $-COOCH_3$), 3.24 (m, 4H, $-SCH_2CH_2S-$), 2.22 (s, 2H, $-COCH_2\overset{|}{\underset{|}{C}}-$), 1.48 (s, 3H, $-CH_3$), 1.06 (s, 3H, $-CH_3$) and 0.90 (s, 3H, $-CH_3$); ms M^+ 328.1166 (calcd. for $C_{16}H_{24}O_3S_2$: 328.1166). Further elution using the same solvent system afforded a diketal (126 mg, 25% yield): ir 1731 cm^{-1} (ester); nmr δ 3.70 (s, 3H, $-COOCH_3$), 3.24 (m, 8H, $-SCH_2CH_2S-$), 1.48 (s, 3H, $-CH_3$), 1.06 (s, 3H, $-CH_3$) and 0.90 (s, 3H, $-CH_3$); ms M^+ 404.0975 (calcd. for $C_{18}H_{28}S_4O_2$: 404.0974).

Keto ester **88** from thioketal **92**

Freshly prepared Raney nickel (5 mL, settled volume) was added to thioketal **92** (308 mg, 0.94 mmol) in 98% ethanol (10 mL). The reaction mixture was stirred at room temperature under an argon atmosphere for 2 h. The mixture was then carefully filtered and residue washed with ethanol (2 x 2 mL). The filtrate was concentrated, then purified by flash chromatography eluting with 5% ethyl acetate in petroleum ether to afford keto ester **88** (115 mg, 52% yield). The spectra were identical to those previously obtained (vide supra).

9,9-Ethylenedioxy-3-hydroxymethyl-3,7,7-trimethylbicyclo[4.3.0]nonane (96)

At 0°C, to a solution of 3.4 M sodium bis(2-methoxyethoxy)aluminium hydride (Red Al) (0.146 mL, 0.496 mmol) in ether (2 mL) was added ketal **91** (46.6 mg, 0.165 mmol) under an argon atmosphere. The reaction mixture was stirred at room temperature for 2 h. It was then cooled to 0°C and ice-cold water added dropwise. The resulting solution was extracted with dichloromethane and ether. The combined extracts were dried, filtered and concentrated. Column chromatography of the residue on silica gel, eluting with 15% ethyl acetate in petroleum ether gave hydroxy ketal **96** (39.8 mg, 95% yield): ir 3480 cm^{-1} (alcohol); nmr δ 3.87 (m, 4H, $-OCH_2CH_2O-$), 3.76 (br, s, 2H, $-C\underline{H_2}OH$); 1.78 (s, 2H, $-CH_2C(CH_3)_2-$), 1.16 (s, 3H, $-CH_3$), 1.02 (s, 3H, $-CH_3$) and 0.94 (s, 3H, $-CH_3$); ms M^+ 254.1881 (calcd. for $C_{15}H_{26}O_3$: 254.1881).

9,9-Ethylenedioxy-3-formyl-3,7,7-trimethylbicyclo[4.3.0]nonane (97)

A solution of pyridinium chlorochromate (44.6 mg, 0.207 mmol) and sodium acetate (3.4 mg, 0.041 mmol) in dry dichloromethane (3 mL) was stirred at room temperature under an argon atmosphere for 20 min. Hydroxy ketal **96** (35 mg, 0.138 mmol) was added and stirring continued for

1.5 h. The reaction mixture was filtered and washed with petroleum ether (2 mL). The filtrate was then concentrated. Column chromatography of the residue on silica gel, eluting with 15% ethyl acetate in petroleum ether afforded ketal aldehyde **97** (27 mg, 78% yield): ir 2830, (aldehyde) and 1739 cm^{-1} (carbonyl); nmr δ 9.38 (br, s, -CHO), 3.86 (m, 4H, $-OCH_2CH_2O-$), 1.76 (s, 2H, $-C\underline{H}_2C(CH_3)_2-$), 1.10 (s, 3H, $-CH_3$), 1.04 (s, 3H, $-CH_3$) and 0.96 (s, 3H, $-CH_3$); ms M^+ 252.1724 (calcd. for $C_{15}H_{24}O_3$: 252.1725).

4-Carbomethoxy-6-carbomethoxyethyl-3,3-ethylenedithio-4,9,9-trimethylbicyclo[4.3.0]nonan-7-one (**101**)

A. Using sodium hydride as base

To a suspension of sodium hydride (80% dispersion in oil, 21.1 mg, 0.7 mmol) in 5 mL of tetrahydrofuran was added a solution of ketal **92** (192 mg, 0.5 mmol) in tetrahydrofuran (1 mL). The mixture was stirred for 30 min at room temperature under an argon atmosphere. Methyl acrylate (0.063 mL, 0.7 mmol) and a drop of tert-butanol were added and stirring was continued for 36 h. Water was added and the resulting solution extracted with dichloromethane. The extract was washed with aqueous saturated sodium chloride solution, dried, filtered and concentrated. Column chromatography of the residue on silica gel, eluting with 10% ethyl acetate in petroleum ether gave pure starting material **92** (163 mg, 85% recovery). The ir, nmr and mass spectra were identical to those previously obtained. Further elution using the same solvent system afforded diester **101** (17 mg, 7% yield): ir 1739 cm^{-1} (ketone and esters); nmr δ 3.72 (s, 3H, $-COOCH_3$), 3.68 (s, 3H, $-COOCH_3$), 3.25 (m, 4H, $-SCH_2CH_2S-$), 2.22 (m, 2H, $-COCH_2\overset{|}{\underset{|}{C}}-$), 1.34 (s, 3H, $-CH_3$), 1.25 (s, 3H, $-CH_3$) and 1.14 (s, 3H, $-CH_3$); ms M^+ 414.1535 (calcd. for $C_{20}H_{30}S_2O_5$: 414.1535).

B. Using potassium hydride as base

Potassium hydride (35% dispersion in mineral oil, 61.2 mg, 0.53 mmol) was washed with petroleum ether (3 x 3 mL) and tetrahydrofuran (5 mL) added. A solution of ketal **92** (146 mg, 0.45 mmol) and a drop of tert-butanol were added and the solution stirred under an atmosphere of argon at room temperature for 30 min. Methyl acrylate (0.048 mL, 0.53 mmol) was added and the solution stirred for 36 h. Ice-cold water was added and the resulting mixture extracted with dichloromethane. The extracts were washed with aqueous saturated sodium chloride solution, dried, filtered and concentrated. Flash chromatography of the residue on silica gel eluting with 10% ethyl acetate in petroleum ether afforded pure starting material **92**

(105 mg, 72% recovery). Further elution using the same solvent system afforded the desired diester **101** (35 mg, 19% yield). The spectral data were identical to those reported previously.

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